Mol Neurobiol (2012) 46:64–77
DOI 10.1007/s12035-012-8253-1

Isoprenoids and Related Pharmacological Interventions: Potential Application in Alzheimer's Disease

Ling Li · Wei Zhang · Shaowu Cheng · Dongfeng Cao · Marc Parent

Received: 9 January 2012 / Accepted: 28 February 2012 / Published online: 15 March 2012

Abstract Two major isoprenoids, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, serve as lipid donors for the posttranslational modification (known as prenylation) of proteins that possess a characteristic C-terminal motif. The prenylation reaction is catalyzed by prenyltransferases. The lipid prenyl group facilitates to anchor the proteins in cell membranes and mediates protein–protein interactions. A variety of important intracellular proteins undergo prenylation, including almost all members of small GTPase superfamilies as well as heterotrimeric G protein subunits and nuclear lamins. These prenylated proteins are involved in regulating a wide range of cellular processes and functions, such as cell growth, differentiation, cytoskeletal organization, and vesicle trafficking. Prenylated proteins are also implicated in the pathogenesis of different types of diseases. Consequently, isoprenoids and/or prenyltransferases have emerged as attractive therapeutic targets for combating various disorders. This review attempts to summarize the pharmacological agents currently available or under development that control isoprenoid availability and/or the process of prenylation, mainly focusing on statins, bisphosphonates, and prenyltransferase inhibitors. Whereas statins and bisphosphonates deplete the production of isoprenoids by inhibiting the activity of upstream enzymes, prenyltransferase inhibitors directly block the prenylation of proteins. As the importance of isoprenoids and prenylated proteins in health and disease continues to emerge, the therapeutic potential of these pharmacological agents has expanded across multiple disciplines. This review mainly discusses their potential application in Alzheimer's disease.

Keywords Isoprenoids · Protein prenylation · Statins · Bisphosphonates · Prenyltransferase inhibitors · Alzheimer's disease

L. Li (✉) · W. Zhang · S. Cheng · D. Cao · M. Parent
Department of Experimental and Clinical Pharmacology,
University of Minnesota,
2001 6th St SE, MTRF 4-208,
Minneapolis, MN 55455, USA
e-mail: lil@umn.edu

Introduction

Isoprenoids are short-chain lipid molecules produced in the mevalonate pathway (Fig. 1) [1]. They include isopentenyl pyrophosphate (IPP), farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP). FPP and GGPP serve as lipid donors for the posttranslational modification (known as prenylation) of proteins that possess a characteristic C-terminal motif, CAAX, in which a cysteine (C) residue is followed by two small aliphatic (A) residues and a variable (X) residue. Prenylation occurs at the C residue with the attachment of either farnesyl or geranylgeranyl group catalyzed by prenyltransferases: farnesyl transferase (FT) and geranylgeranyl transferase type I (GGT-I) and II (GGT-II or RabGGT). The X residue contributes significantly to the specificity of prenyltransferases [2]. The lipid prenyl group facilitates to anchor the proteins in cell membranes and mediates protein–protein interactions. A variety of important intracellular proteins including heterotrimeric G protein subunits and nuclear lamins are prenylated but the largest, and most extensively studied group, is the small GTPase superfamilies including the well-known Ras, Rab, Rho, and Rac [3]. Small GTPases are essential signaling proteins that regulate a variety of cellular processes and functions, such as cell growth, differentiation, cytoskeletal organization and vesicle trafficking. The prenylation status of small GTPases affects their intracellular trafficking, subcellular

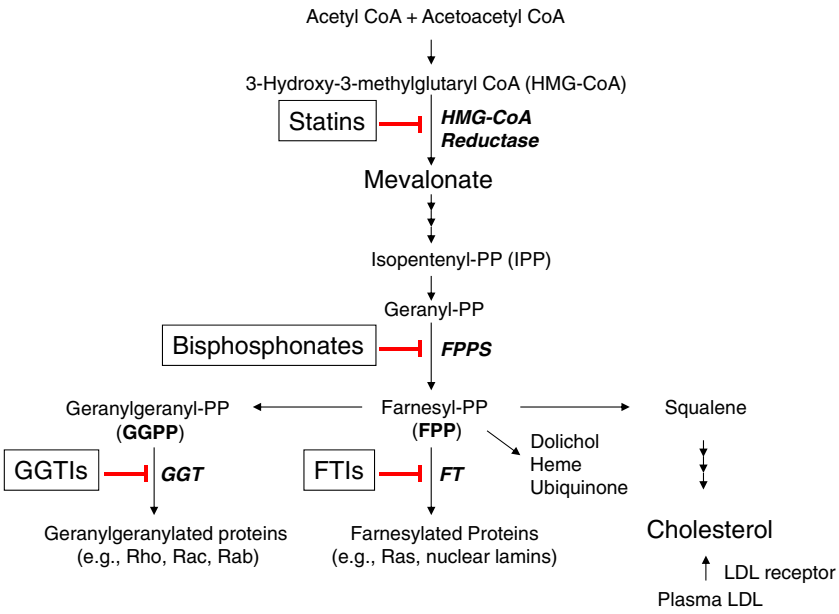

Fig. 1 The mevalonate pathway. Pharmacological agents inhibit the activity of key enzymes in the mevalonate pathway [1] and elicit a series of metabolic and functional changes of downstream molecules (see text for details). *PP* pyrophosphate, *FPPS* farnesyl PP synthase, *FT* farnesyl transferase, *FTIs* farnesyl transferase inhibitors, *GGT* geranylgeranyl transferase, *GGTIs* geranylgeranyl transferase inhibitors

localization and interactions with substrates. Therefore, prenylation modifies the functions of small GTPases as well as the functions of their downstream effectors. Prenylated proteins have been found to play a critical role in the development of some cancers and other diseases including cardiovascular and cerebrovascular diseases, bone diseases, Alzheimer's disease (AD), and progeria. Consequently, isoprenoids and/or prenyltransferases have emerged as attractive therapeutic targets. This review attempts to summarize the pharmacological agents currently available or under development that control isoprenoid availability and/or the process of prenylation, i.e., statins, bisphosphonates, and prenyltransferase inhibitors, and their potential therapeutic applications, focusing on Alzheimer's disease.

Statins

Statins are a class of drugs that have been successfully used for the treatment of hypercholesterolemia and the prevention of coronary heart disease in the last 20 years [4, 5]. Statins selectively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate limiting enzyme of the mevalonate pathway (Fig. 1) [1], which is the principal cholesterol biosynthesis pathway in eukaryotic cells. By targeting HMG-CoA reductase, statins block the conversion of HMG-CoA into mevalonate, the initiating step of cholesterol biosynthesis, and thus lower the production of downstream molecules including isoprenoids and cholesterol. In the liver, the reduced intracellular cholesterol level induces the up-regulation of LDL (low-density lipoprotein) receptors that thereby restore the intracellular cholesterol homeostasis, which subsequently promotes the clearance of cholesterol-loaded LDL in the blood [6].

Several statins have been approved by the US Food and Drug Administration (FDA; Table 1). These statins vary in their derivation, physical properties, pharmacology, and pharmacokinetics. Lovastatin is a natural product of a fungus *Aspergillus terreus*, whereas others are produced by chemical modification of lovastatin (such as simvastatin and pravastatin) or by chemical synthesis (such as atorvastatin, fluvastatin, rosuvastatin, and pitavastatin) [7, 8]. Each of the statins has a characteristic structure that interacts with the binding site of HMG-CoA reductase [9], inhibiting the enzyme activity and the production of downstream molecules. Although all statins share a common mechanism for inhibiting HMG-CoA reductase, they differ in terms of their potency and their ability to cross the blood-brain barrier (BBB; Table 1) [7, 8, 10, 11].

A large body of evidence indicates that the beneficial effects of statins in preventing coronary heart disease extend beyond their cholesterol-lowering ability [12]. Cholesterol-independent (pleiotropic) effects of statins have been shown in a number of in vitro, animal models and clinical studies, such as reducing the risk of stroke [13], osteoporosis [14], and multiple sclerosis [15]. Many of the pleiotropic effects of statins are shown to be mediated through inhibition of the synthesis of isoprenoid intermediates, such as FPP and GGPP, in the mevalonate pathway (Fig. 1).

More recently, epidemiological studies show that statins decrease the risk of AD although prospective studies have produced mixed results. The discrepancies among these studies most likely are caused by differences in the choice and dose of statins, the selection of patient populations, the

Table 1 FDA-approved statins

Generic name	Brand name	Lipophilic/ hydrophilic	BBB permeability	$T_{1/2}$ (h)	Metabolism (CYP)	LDL-C reduction (%)[a]	Approval Date
Lovastatin	Mevacor®	Lipophilic	High	2–3	3A4	34	Aug 31, 1991
Pravastatin	Pravachol®	Hydrophilic	Low	1.5–2	3A4 (min)	34	Oct 31, 1991
Simvastatin	Zocor®	Lipophilic	High	2	3A4	41	Dec 23, 1991
Fluvastatin	Lescol®	Lipophilic	Low	1	2 C9	24	Dec 23, 1993
Atorvastatin	Lipitor®	Lipophilic	Low	14	3A4	50	Dec 17, 1996
Rosuvastatin	Crestor®	Hydrophilic	Low	20	2 C9 (min)	63	Aug 12, 2003
Pitavastatin	Livalo®	Lipophilic	Low	12	2 C9 (min)	48	Aug 9, 2009

Modified from reference [7, 8, 10, 11]

BBB blood-brain barrier, *CYP* cytochrome P450, *LDL-C* low-density lipoprotein cholesterol

[a] The effect was obtained in hyperlipidemic patients by a daily dose of 40 mg of all statins except for pitavastatin (4 mg) [10]

treatment durations, and the criteria of outcome measures (recently reviewed by Shepardson et al. [16]). Since epidemiological studies have demonstrated a correlation between high cholesterol levels and the incidence of AD [17–19], some of the benefits of statins in AD could be attributed to the well-established cholesterol-lowering function of statins. Indeed, several in vitro and in vivo studies have shown that statins modulate the processing of amyloid-β precursor protein (APP) and decrease the production of amyloid-β peptide (Aβ) through lowering the cellular cholesterol content [20–22]. However, emerging evidence indicates that beneficial effects of statins in AD are not limited to lowering levels of cholesterol. The isoprenoid-dependent pleiotropic effects of statins may also contribute to their role in AD therapy as summarized below.

Effects on APP/Aβ Metabolism

One of the pathological hallmarks of AD is the deposition of aggregated Aβ in neuritic plaques and cerebral vessels. Aβ (38–43 amino acids) is derived from a large transmembrane glycoprotein, APP, by proteolytic processing. The generation of intact Aβ requires the activity of both β-secretase and γ-secretase, which cleave within the luminal and transmembrane domain of APP, respectively. The α-secretase cleaves within the sequence of Aβ, thus precluding the formation of intact Aβ (non-amyloidogenic processing of APP), and produces the neurotrophic soluble fragment, sAPPα [23].

A number of studies have shown that statins affect APP processing and Aβ production through isoprenoid-dependent pathways as well as cholesterol-dependent pathways. Atorvastatin and simvastatin were found to stimulate α-secretase activity and shedding of non-amyloidogenic sAPPα by depleting FPP and inhibiting farnesylation of Rho and Rho kinase in a murine neuroblastoma cell line [24]. In contrast, other in vitro studies reported that lovastatin or simvastatin augments intracellular accumulation of APP and Aβ, in parallel with a decrease of secreted Aβ, in a GGPP-dependent manner [25–27]. The mechanisms proposed include the increase/activation of β-secretase [25], inhibition of vesicle trafficking [26], and inhibition of γ-secretase activity [27]. However, a recent study showed that statins decrease Aβ levels only by lowering cellular cholesterol levels rather than the levels of FPP/GGPP or prenylation in a human neuroblastoma cell line [28]. In vivo, many studies found no significant changes in the level/deposition of Aβ with statin treatments (reviewed in [29]), while the beneficial effects of statins were still observed. We have demonstrated that simvastatin enhances spatial learning and memory without affecting the level/deposition of Aβ in a transgenic mouse model of AD, Tg2576 mice [30]. A careful comparison of published experimental studies revealed that reduction of Aβ was only observed in the studies where a high dose of the drug was used and/or the drug treatment was initiated before the manifestation of β-amyloidosis. Yet, a recent study demonstrated that fluvastatin, at clinical doses, significantly reduced the level of Aβ and the C-terminal fragments (CTFs) of APP in the brain of wild-type C57BL/6 mice [31]. The underlying mechanisms include enhanced trafficking of APP-CTFs from endosomes to lysosomes for degradation, associated with marked decrease of prenylated Rab proteins, and increased clearance of Aβ from the brain through upregulation of low-density lipoprotein receptor-related protein 1 (LRP-1) at the blood-brain barrier [31]. Clearly, the effects of statin-induced depletion of isoprenoids on APP/Aβ metabolism are much more complex than previously thought.

Immunomodulatory Effects

Convincing data indicate that innate immunity are involved in the pathogenesis of AD (recently reviewed by [32]). Many inflammation-related proteins, such as immunoglobulins, complement factors, α1-antichymotrypsin, apoE, clusterin,

intracellular adhesion molecule-1, α2-macroglobulin, C-reactive protein, serum amyloid P component, and heparan sulphate proteoglycans, have been identified in senile plaques and neurofibrillary tangles [33–36]. These proteins affect the transport, aggregation, and deposition of Aβ [32]. Conversely, Aβ activates microglia and astrocytes and upregulates the expression of innate immune receptors and secretion of pro-inflammatory cytokines and other inflammatory mediators [37, 38], leading to the activation of the complement system and the initiation of inflammatory cascades. While strong acute immune response could be protective initially, chronic upregulation of certain pro-inflammatory factors could interfere with removal mechanisms of Aβ, exacerbating AD pathology [32]. The importance of immune function in AD is further underscored by findings from recent genome-wide association studies, in which six of the nine new genes that are associated with sporadic AD are also involved in immune functions [39].

Statins possess anti-inflammatory and immune-modulatory properties. In vitro studies have demonstrated that statins regulate pro-inflammatory molecules such as inducible nitric oxide synthase, interleulin-1β (IL-6), and tumor necrosis factor-α (TNF-α) [40]. For instance, pravastatin pretreated human glioma cells show lower IL-6 and free radical expression when exposed to Aβ [41]. Statins reduce the expression of inflammatory cytokines and interfere with leukocyte migration to the central nerve system (CNS) [42]. In cultured microglial cells, lovastatin attenuates microglial activation by suppressing the functional expression of CD40, which prevents Aβ phagocytosis, [43]. Lovastatin also inhibits the expression of TNF and IL-1β [44] and effectively decreases autoimmunity and promotes myelin repair in glial cells [45]. Moreover, microglia cultures exposed to simvastatin and atorvastatin showed reduced level of pro-inflammatory cytokine IL-6 [46]. Recently, it has been shown that simvastatin treatment also prevents Aβ-induced production of interferon-γ (IFN-γ) and enhances the immune responses to Aβ vaccination [47].

Interestingly, despite the extensive reports on anti-inflammatory effects of statins, the impact of statins on the immune system of the CNS remains elusive. While no mechanism dominates the anti-inflammatory effects of statins, they are partly attributable to the inhibition of small GTPase prenylation. For example, statin-mediated inhibition of Rho GTPase leads to the attenuation of Aβ deposit-associated inflammation [48]. Statin treatments also cause the accumulation of un-prenylated, nonfunctional small GTPases and inflammatory inhibition, which can be reversed by the addition of isoprenyl precursor or GGPP [49].

Neuroprotective Effects

Apoptosis-mediated neuron loss represents one of the key detrimental hallmarks in AD pathology. Substantial evidence suggests that statins protect neurons by suppressing Aβ-induced apoptosis. For instance, simvastatin treatment enhances the expression of Bcl-2, a pro-survival molecule, and reverses the Aβ-induced expression of caspase-3 and neuron death. With the addition of Bcl-2 anti-sense oligonucleotides, however, this neuroprotective effect of simvastatin is abolished, suggesting the protective effect is Bcl-2 dependent [50, 51]. In SH-SY5Y cells, rosuvastatin has been shown to curtail the caspase-3 activity by approximately 50 %, while at the same time raising the level of a pro-survival fragment, sAPP-α [52]. In addition, statins protect cultured cortical neurons from excitotoxicity after exposure to *N*-methyl D-aspartate (NMDA) [53] and monosodium glutamate [54]. Furthermore, in a rabbit ischemic stroke model, simvastatin exhibits neuroprotective effects by inhibiting Rho-associated kinase (ROCK) [55], and in a mouse model for Parkinson's disease, simvastatin prevents dopaminergic neuronal loss by inhibiting the activation of Ras [56]. On the contrary, lovastatin has been shown to enhance apoptosis and tau protein phosphorylation in neurons via regulation of the Rho family of GTPase [56, 57]. Interestingly, among all commercially available statins, simvastatin was found to be the most effective at protecting against kainate-induced excitotoxicity and memory impairment [58].

Statins have also been shown to protect neurons from Aβ-associated apoptosis by activating various anti-apoptotic pathways. For example, lovastatin enhances Wnt signaling pathway by stabilizing β-catenin through inhibition of glycogen synthase kinase 3β (GSK-3β) [59], thus protecting against Aβ-induced neurotoxicity [57]. Atorvastatin also promotes neuron survival and plasticity through catenin pathway in a rat model of stroke [60]. Furthermore, simvastatin and lovastatin promote cell survival by activation of phosphoinositide 3-kinase (PI3-K)/Akt pathway and mitogen-activated protein kinase (MAPK) pathway [61, 62]. In addition, atorvastatin increases cell survival by enhancing transforming growth factor β1 (TGF-β1)/Smad signaling pathway [63]. Although the underlying mechanisms by which statins regulate signaling molecules are not fully understood, inhibition of RhoA/Rock pathway has been shown to mediate some of the effects of statins on aforementioned signaling pathways [60, 63].

Effects on Cognitive Function and Synaptic Plasticity

Many studies on the cognitive effects of statins have focused on the potential therapeutic benefits of statins for the treatment of stroke or traumatic brain injury [64–67]. For example, in rat models, chronic administration of atorvastatin or simvastatin following traumatic brain injury have been shown to improve rehabilitation of spatial memory [66], reduce inflammatory cytokine production [64], and improve cerebral blood flow to the injury site [65]. Furthermore, statins stimulate

angiogenesis, neurogenesis, synaptogenesis in treated animals [65, 66], and promote neurite outgrowth in cultured hippocampal neurons [68]. Though, it is noteworthy that several studies indicate that under some conditions (e.g., high concentrations), statins may decrease neurite outgrowth or synaptogenesis [69–71]. Recently, the therapeutic potential of statins in AD has been investigated, largely prompted by the findings from epidemiological studies that show a markedly lower prevalence of AD/dementia in statin-prescribed populations [72, 73]. However, while some prospective studies showed that statin treatment improved cognitive function in normocholesterolemic patients [74] or slowed the decline in cognitive function of AD patients [75], others show no protection of statins in preventing AD in a group of patients at risk for cardiovascular disease[76, 77]. In rare cases, use of statin has also been associated with cognitive impairment [78]. The possible reasons for such discrepancy have been reviewed thoroughly recently [16, 79]. Experimentally, we reported that chronic simvastatin treatment rescued hippocampal-dependent learning and memory in a transgenic mouse model of AD independent of changes in Aβ pathology [30]. Interestingly, dramatic memory improvements were also observed in non-transgenic wild-type littermate controls [30], indicating a general pro-cognitive effect on brain function. A similar effect has been observed in adult rats treated with simvastatin for 25 days prior to testing in passive avoidance or object-in-place tasks [80].

In mammalian systems, the molecular and cellular changes mediating the induction and maintenance of long-term potentiation (LTP), a long-lasting synaptic enhancement, in the hippocampus are widely considered to be the basis for explicit memory formation and storage [81]. In AD, dysfunction of cholinergic and glutamatergic synapses in the hippocampus and neocortex occurs prior to apparent neuronal degeneration [82]. Thus, rescuing synaptic function could be an effective early intervention against AD. Atorvastatin has been shown to increase synaptic plasticity in the hippocampus of rats following acute in vivo administration of Aβ [83]. However, these potentially beneficial effects of statins are countered by a report that acute in vitro treatment of mouse hippocampal slices with mevastatin (also known as compactin; a statin not approved for human use) inhibits LTP at CA3-CA1 synapses [84, 85]. Recently, we have demonstrated that treatment of hippocampal slices for several hours with simvastatin increases the magnitude of *N*-methyl-D-aspartic acid receptor (NMDAR)-dependent LTP in the CA1 region in the hippocampus of adult wild-type mice [86, 87]. The reasons for the discrepancy between the studies may be related to the differences in the type of statins, the LTP induction protocols, and the age of the animals used [86].

The molecular mechanisms underlying the effects of statins on synaptic plasticity and cognitive function have not been fully elucidated. Likely, statins exert their pro-synaptic/pro-cognitive effects through multiple pathways (Fig. 2). We have shown that enhancement of learning and memory by chronic simvastatin treatment is associated with an increased level of activated (phosphorylated) Akt (p-Akt) in the brain of wild-type mice [30]. Consistent with our results, the PI3-K/p-Akt signaling pathway has been implicated in synaptic plasticity and memory consolidation [88]. Recently, we further demonstrated that a PI3-K inhibitor, LY-294002, selectively reduces LTP in simvastatin-treated slices [86], suggesting that PI3-K signaling is necessary for simvastatin-induced LTP enhancement.

Several lines of evidence indicate that statin-induced depletion of isoprenoids and subsequent inhibition of small GTPase prenylation are responsible for modulating cognitive and synaptic functions. In a mouse model of neurofibromatosis type 1 (NF1) mental retardation, caused by excessive p21 Ras activity, lovastatin normalizes p21Ras activity and reverses deficits in LTP and spatial learning [89]. Consistently, several other studies have shown that Ras negatively regulates NMDAR transmission. H-Ras overexpression decreases tyrosine phosphorylation of NMDAR NR2A subunit and the magnitude of LTP [90], and inhibiting a Ras effector protein, RACK1, increases NMDAR currents in hippocampal neurons [91]. Conversely, H-Ras-deficient mice display enhanced tyrosine phosphorylation of NMDAR NR2A and NR2B subunits that occurs with an accompanying increase in NMDAR conductance and LTP magnitude [92]. These findings strongly suggest that statin-mediated Ras inhibition could account for the augmentation of NMDAR-dependent plasticity in statin-treated animals. Recently, we found that the LTP-enhancing property of simvastatin is specifically blocked by supplementation of FPP, the substrate for farnesylation [87]. Our observations corroborate several reports [89–92] demonstrating a negative relationship between NMDAR-dependent synaptic plasticity and the farnesylation pathway. As the brains of AD patients produce elevated amounts of FPP and GGPP [93], it is plausible that elevated isoprenoid production may be directly detrimental to synaptic and cognitive function, and therefore statins may present a potential treatment for synaptic and cognitive disorders.

Bisphosphonates

Bisphosphonates (BPs) are chemically stable analogues of natural pyrophosphate compounds that normally prevents calcification of soft tissues, and regulates bone mineralization [94]. BPs had been available hundreds of years but it was only 40 years ago that they were discovered as effective inhibitors of bone resorption [95, 96]. Since then, numerous BPs have been synthesized and many of them are approved

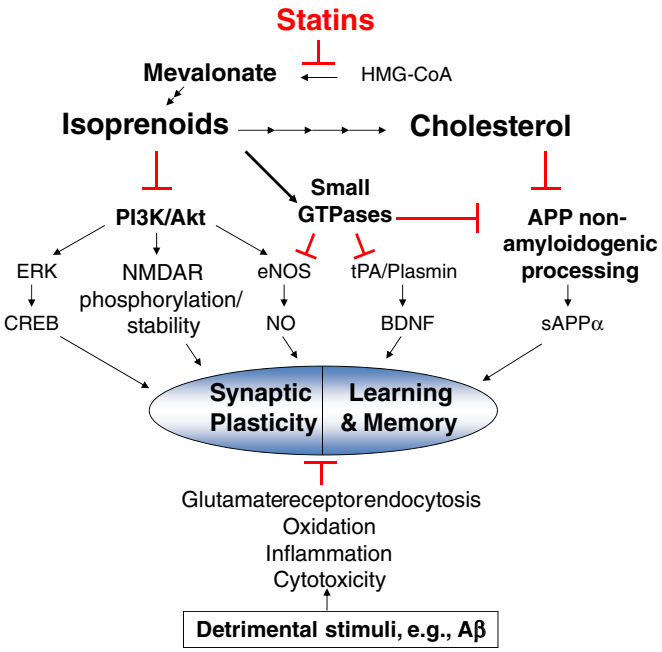

Fig. 2 Potential pathways by which statins exert pro-synaptic/pro-cognitive effects. Statins may counteract detrimental effects of noxious stimuli such as amyloid-β (Aβ) through multiple pathways [13, 30, 83, 86, 87, 158–164]. *PI3K/Akt* phosphoinositide 3-kinase/protein kinase B; *ERK* extracellular signal regulated kinase; *CREB* cAMP response element binding protein; *NMDAR* *N*-methyl-D-aspartic acid receptor; *NO* nitric oxide; *eNOS* endothelial nitric oxide synthase; *tPA* tissue-type plasminogen activator; *BDNF* brain-derived neurotrophic factor; *sAPPα* neurotrophic fragment produced by α-secretase cleavage of amyloid-β precursor protein

for treating bone diseases of excessive bone resorption [97]. Based on their mechanisms of action, BPs can be categorized into two groups: the non-nitrogen BPs and nitrogen-containing BPs. The non-nitrogen BPs, such as etidronate and clodronate, have simple chemical structures. They act by incorporating into toxic, non-hydrolyzable ATP analogues [98]. The more potent, nitrogen-containing BPs (N-BPs), such as pamidronate, neridronate, risedronate, zoledronate, minodronate, alendronate, and ibandronate, inhibit the enzymes in the mevalonate pathway [98]. The main target of N-BPs is farnesyl pyrophosphate synthase (FPPS), downstream of HMG-CoA reductase where statins act (Fig. 1). This section will be focused on the current state of research on N-BPs (Table 2).

Mechanisms of Action of N-BPs

The therapeutic application of N-BPs attributes to the properties common to all BPs: their backbone P–C–P structure and the ability to chelate calcium ions. Therefore, they are targeted rapidly to bone mineral surface in vivo, where they are taken up mainly by osteoclasts (bone-destroying cells). Emerging evidence, however, indicates that other endocytic cells such as monocytes and macrophages may also internalize BPs that are present transiently in the circulation [99]. Once inside the cell, N-BPs, through yet an unknown intracellular pathway, bind FPPS and inhibit its activity, leading to a depletion of FPP and GGPP. Consequently, the

Table 2 FDA-approved nitrogen-containing bisphosphonates

Generic name	Brand name	IC_{50} (nM)[a]	Bone binding affinity (μM)[b]	Metabolism[c]	Approval date
Pamidronate	Aredia®	200	83	None	Oct 31, 1991
Alendronate	Forsamax®	50	61	None	Sep 29, 1995
Risedronate	Actonel®	10	85	None	Mar 27, 1998
	Atelvia®				Oct 8, 2010
Zoledronate	Zometa®	3	81	None	Aug 20, 2001
	Reclast®				Apr 16, 2007
Ibandronate	Boniva®	20	116	None	May 16, 2003

[a] Analyses of FPPS inhibition were conducted with recombinant human enzyme [155]

[b] Binding affinity of N-BPs for human bone [156]

[c] No enzymes capable of cleaving the P–C–P bond have been discovered. N-BPs are absorbed, stored, and excreted from the body unaltered [157]. The biological half-life of N-BPs in the blood is very brief as they rapidly bind to bone, whereas their retention in the skeleton may last a lifetime

prenylation process is impaired, causing loss of membrane attachment of proteins such as small GTPases, loss of interactions with other proteins and downstream signaling, and/or accumulation of unprenylated proteins and therefore inappropriate activation of downstream signaling pathways. Concurrently, inhibition of FPPS also results in the accumulation of upstream metabolite IPP (Fig. 1), which leads to the formation of new metabolites such as ApppI (an ATP analog) [98]. Although N-BPs may act on additional molecular targets, these two mechanisms, inhibition of protein prenylation and accumulation of ApppI, are mainly responsible for the anti-resorptive and apoptosis-inducing effects of these agents on osteoclasts [98]. By inhibiting bone resorption and inducing osteoclast apoptosis, N-BPs reduce bone turnover, increase bone mass, and improve bone mineralization.

Interestingly, the effects of N-BPs on osteoclasts are mediated primarily through inhibition of protein geranylgeranylation rather than protein farnesylation, even though N-BPs depletes both GGPP and FPP. This is supported by experiments in which supplementation of geranylgeraniol, which is readily converted to GGPP for protein geranylgeranylation, but not farnesol, which is readily converted to FPP for protein farnesylation, abolishes the effects of N-BPs on inhibiting osteoclast formation and bone resorption [100]. Additional evidence comes from studies in which specific prenylation inhibitors were used. Whereas loss of geranylgeranylated proteins in osteoclasts in the presence of a GGT inhibitor blocks bone resorption, loss of farnesylated proteins in the presence of an FT inhibitor has little effect [101]. Therefore, geranylgeranylated proteins appear to play a significantly more important role in regulating the functions of osteoclasts than farnesylated proteins.

Potential Applications of N-BPs in Diseases Other Than Bone Disorders

Therapeutic applications of N-BPs in other conditions are limited by their rapid targeting to bone. However, studies have shown that N-BPs possess strong anti-tumor activities in vitro and in some in vivo models of cancer through FPPS inhibition in tumor cells [102]. Additionally, N-BPs may have therapeutic potential for Hutchinson–Gilford progeria syndrome (HGPS), caused by mutations in nuclear lamin A protein and subsequent accumulation of prenylated mutant lamin A [103, 104]. Treatment of N-BPs in combination with statins was found to attenuate the aging symptoms and extends longevity in a mouse model of HGPS [105]. The combined treatment effectively inhibits the prenylation process and therefore blocks abnormal membrane localization and function of mutant lamin A in the nucleus of HGPS cells [105]. Furthermore, some evidence indicates that N-BPs may have positive effects on neurodegenerative disorders such as Alzheimer's disease. An in vitro study shows that N-BPs prevent the oxidative stress-induced inactivation of human brain muscarinic acetylcholine receptors exposed to Alzheimer's brain extract [106]. An animal experiment demonstrates that a BBB permeable N-BP suppresses the activity of acetylcholinesterase (AchE) in the frontal cortex of rats [107], implicating the potential benefits of N-BPs in AD as AchE inhibitors are commonly used to treat patients with AD. The recent finding that levels of FPP and GGPP are elevated significantly in the brain of Alzheimer's patients [93] also suggests that treatment with FPPS inhibitors to reduce downstream isoprenoids may provide therapeutic benefits. However, development of prodrugs of N-BPs or other types of FPPS inhibitors, which circumvent the tissue distribution limitations of these compounds, will be necessary for clinical use of these drugs in treating neurological disorders. Alternatively, a drug delivery vehicle can be developed to deliver and protect N-BPs until they are released in the CNS.

Much effort has been made to remove the phosphonate groups of N-BPs so that they would be accessible to other tissues. Interestingly, even subtle modifications to the phosphonate groups (such as methylation) that reduce binding to bone mineral also decrease the ability of these compounds to inhibit protein prenylation because the phosphonate groups appear to be critical for interacting with the substrate binding site of FFPS [108–110]. Recently, novel non-BP inhibitors of FPPS that bind to an allosteric site on the enzyme have been identified [111]. These inhibitors lack the phosphonate groups of N-BPs and thus do not bind to bone mineral, offering the hope that this new class of compounds may lead to a much broader therapeutic applications of FPPS inhibitors clinically.

Prenyltransferase Inhibitors

As discussed above, both statins and N-BPs function by limiting the availability of prenylation substrates, FPP and GGPP. Therefore, they affect protein prenylation broadly and nonspecifically. Prenylation reactions are catalyzed by one of the three prenyltransferases: FT, GGT-I, and GGT-II. While protein targets for FT and GGT-I include CAAX-containing farnesylated proteins (Ras, nuclear lamins, and others) and geranylgeranylated proteins (Rho/Rac families and others), respectively, Rab protein family members are exclusive substrates of GGT-II, of which much less is known [112]. To target the prenylation of certain proteins, selective inhibitors have been developed to curtail the activity of FT and GGT-I specifically and several of them are in clinical trials [113, 114] (Table 3).

Farnesyl Transferase Inhibitors

Initial interest in developing farnesyl transferase inhibitors (FTIs) was prompted by the finding that approximately 30 %

Table 3 Prenyltransferase inhibitors in clinical trials

Drug	Other name(s)	Chemical derivative	IC_{50} (nM)	Phase	Trials[a]	Diseases
FTIs						
Tipifarnib	R115777 Zarnestra	Imidazole-methylquinolinone	1–8	I, II, III	80	Cancers
Lonafarnib	SCH66336	Tricyclic	1–10	I, II, III	28	Cancers
	Sarasar	carboxamine			3	Progeria
					1	Heptitis D
BMS-214662		Tetrahydro-benzodiazepine	1–8	I	6	Cancers
L-778,123		Peptidomimetic	2	I	2	Cancers
GGTI						
GGTI-2418		Peptidomimetic	9.5	I		Cancers

Information based on references [113, 114]

[a] The number of clinical trials documented at www.ClinicalTrails.gov

of all human cancers harbor activating oncogenic mutations in the Ras genes (mainly H-Ras, K-Ras, and N-Ras) and that farnesylation was absolutely required for the malignant transforming activity of mutated Ras GTPases [115]. The importance of farnesylation in tumorigenesis is underscored recently by tissue-specific genetic deletion of FT in mouse models, in which the mutant K-Ras-induced lung cancer is hampered and the lifespan extended [116], further validating the efforts of developing FTIs as anti-cancer therapies.

A variety of FTIs have been developed and investigated in anticancer clinical trials. These include peptide analog inhibitors that mimic and compete with substrates of FT, CAAX-containing proteins or FPP, as well as nonpeptidomimetic inhibitors or compounds that were identified from high throughput screening of large compound libraries. Several FTIs, including tipifarnib, lonafarnib, BMS-214662, and L-778,123, have been or are being evaluated in clinical trials (Table 3). FTI treatment results in the reversal of several hallmarks of cancer, including mitotic arrest at prometaphase [117, 118], induction of apoptosis [119, 120], inhibition of anchorage-dependent and anchorage-independent growth [121], reduction of invasion and angiogenesis [122, 123], and induction of tumor regression in animal models. Although preclinical studies indicate that FTIs are highly effective as anti-cancer agents, clinical trials with FTIs have only produced limited success (recently reviewed in [113]). The reason for such poor clinical outcome is not completely clear but partly due to the lack of complete understanding on the mechanism of action of FTIs and the obscurity of specific farnesylated proteins critical for the development of certain cancers. Another possibility relates to the fact that K-Ras and N-Ras can be geranylgeranylated by GGT when FT is inhibited and remain fully functional [124–126], therefore escaping the inhibition by FTIs. This situation prompts the effort of developing GGT inhibitors (geranylgeranyl transferase inhibitors (GGTIs); discussed below).

The application of FTIs has extended beyond cancers. As with statins and N-BPs, FTIs have been shown to offer beneficial effects on Hutchinson-Gilford progeria syndrome (HGPS), in which mutant lamin A protein remains persistently farnesylated and anchored in the nuclear membrane, leading to its aberrant behavior during interphase and mitosis [103, 104]. Numerous studies have shown that treating HGPS cells with FTIs can block, and possibly even reverse, abnormalities caused by mutant lamin A (recently reviewed by in [127]). Furthermore, in animal models of HGPS, treatment with an FTI (ABT-100) has also been found to attenuate several of progeroid phenotypes with respect to body weight, fat deposition, and bone density, and increased life expectancy [128, 129]. A more recent study demonstrated that treatment with an FTI (R115777, Zarnestra) retards the onset, as well as the progression, of cardiovascular diseases in the human mutant lamin A transgenic mouse model [130]. These successful findings in animal models are the driving force for the initiation of clinical trials using FTIs to ameliorate or reverse the disease process in progeria children [131]. In addition, a short-term treatment with an FTI has been shown to aid the therapy for cardiovascular disease by inhibiting neointima formation and preventing restenosis after balloon angioplasty [132].

The therapeutic potential of FTIs for parasitic diseases (such as malaria) has also been explored [133]. These FTIs have been designed specifically to inhibit parasitic FT but not mammalian FT [134, 135]. In addition, some viruses (such as hepatitis D virus) depend on protein farnesylation for their virion assembly. Thus, FTIs have been tested for their antiviral activity and shown to be highly effective at clearing viremia in mice infected with hepatitis D virus [136], suggesting their potential as an antiviral agent.

A potential neurological application of FTIs has also emerged recently. FTIs have been used to rescue synaptic and cognitive deficits caused by overactivation of farnesylated

proteins. For instance, members in the Ras superfamily, many of which depends on farnesylation for their function, play important roles in neuronal plasticity and memory formation [137]. Treatment with an FTI (BMS 191563) attenuates the activity of mutant Ras and reverses learning and memory impairment in a mouse model of NF1[138]. As discussed earlier, farnesylation of H-Ras negatively regulates synaptic plasticity [90–92] and genetic deletion of H-Ras leads to the enhancement of hippocampal LTP [92]. Consistent with these findings, recently we have shown that an FTI (FTI-277) enhances the magnitude of LTP in the hippocampus of WT mice [87], implicating the potential of FTIs as a modulator of synaptic function even under normal non-diseased conditions. Whether FTIs have any effects on the development of Alzheimer's disease has not been investigated. However, the recent finding that the level of FPP is elevated in the brain of AD patients [93] suggests that the abundance of farnesylated proteins could be increased, contributing to the pathogenesis of AD. Therefore, use of FTIs could potentially offer beneficial effects on AD. In addition to small GTPases, FTIs can modify the function of other farnesylated proteins. Recently, an FTI (FTI-277) was found to attenuate alpha-synuclein-induced neurotoxicity by reducing the membrane association of farnesylated ubiquitin C-terminal hydrolase-L1 (UCH-L1) that is linked to Parkinson's disease (PD) and memory [139].

Geranylgeranyl Transferase Inhibitors

The finding that some farnesylated proteins, such as K-Ras and N-Ras, can escape FTI-mediated inhibition and remain fully functional via geranylgeranylation by GGT underscores the importance of developing GGTIs, as well as FTIs, for cancer therapy. The benefits of simultaneous inhibition of FT and GGT against tumorigenesis were further supported by conditional knockout mouse models, in which simultaneous ablation of FT and GGT produced a far greater effect on mutant K-Ras induced lung cancer onset and progression than either deletion alone [116]. Several GGTIs have been developed, and similar to FTIs, GGTIs have been shown to inhibit tumor cell growth in cultured cells and in animal models [113]. One GGTI (GGTI-2418) is currently being tested in clinical trials ([140]; Table 3).

The application of GGTIs in diseases other than cancers has also been explored. GGTIs may be able to facilitate the therapy for cardiovascular disease by blocking neointima formation after balloon angioplasty and improving endothelial function (upregulation of nitric oxide synthase), through inhibition of RhoA and Rac1 [141, 142]. Also, several studies have shown that GGTIs can directly act on neuronal cells and the central nervous system. In rat hippocampal neurons, a GGTI (GGTI-286) enhances neuritogenesis [68]. Similarly, GGTI-286 promotes neurite outgrowth in the culture of rat embryonic cortex explants and postnatal spinal cord explants, suggesting its potential in promoting axon regeneration in brain and spinal cord injury [143]. Another GGTI, GGTI-298, has been shown to enhance survival, proliferation, and differentiation of cultured glial cells and promote myelin repair in a rat model of experimental autoimmune encephalomyelitis [45]. In addition, the fact that more proteins are subjected to geranylgeranylation than farnesylation [144] suggests that GGTIs could play an even broader modulatory role than FTIs. For example, small GTPases such as Rho and Rac, which require geranylgeranylation to function properly, are implicated in regulating APP/Aβ metabolism [25–27], neuronal migration and development [145], axon extension and dendritic structure [146], and neuronal plasticity and memory formation [147]. Therefore, GGTIs may be a potential therapeutic agent for AD and other cognitive impairment disorders.

Conclusions and Perspectives

Development of isoprenoid- and prenylation-related interventions has been spurred by the importance of growing numbers of prenylated proteins in health and disease [148]. Although remarkable progress has been made toward the treatment of cardiovascular and bone diseases and some forms of cancers, the full therapeutic potential of isoprenoid- and prenylation-related agents remains to be achieved.

One of the challenges facing the field of prenylation is the enormous scope and complexity of prenylated proteins. Even though numerous biologically important proteins have been identified to undergo prenylation [2], the exact size of the prenylome is unknown [149]. Based on the literature, several hundred proteins are subjected to prenylation [113, 148]. The impact of prenylated proteins certainly extends beyond what has been shown experimentally. Most of the studies have focused on the prenylation of individual proteins and therefore have only touched the tip of the iceberg. Recently, methods are being developed to characterize protein prenylation globally. One approach is to label cellular proteins with detectable FPP and/or GGPP analogs [150–154] and another approach uses a sequence-based computer program specially designed to predict if proteins are prenylated [149]. Application of these approaches will enable a quantitative proteome-wide analysis of the regulation of protein prenylation and its modulation by therapeutic agents. Also, as these techniques become feasible in general laboratories and clinics, prenylomic profiling of individuals can be performed to facilitate personalized medicine, decoding inter-individual differences in the response to therapeutic agents.

Finally, to develop highly selective and effective therapeutic agents, it will be crucial to identify specific prenylated

proteins that play critical roles in the pathogenesis of relevant diseases. Recently generated conditional knockout mice, in which FT and GGT activities can be ablated in a tissue-specific manner [116], provide an invaluable in vivo model system to investigate the entire spectrum of influence of prenylation inhibition. In conjunction with aforementioned approaches to characterize the prenylome, these animal models offer an unprecedented opportunity for elucidating the mechanisms of disease, identifying and validating therapeutic targets, and ultimately improving the outcomes of clinical trials.

Acknowledgments This work was supported in part by grants from the National Institutes of Health (AG031846), the Alzheimer's Association (IIRG-09-131791, the American Health Assistance Foundation (A2010328), and the Academic Health Center of the University of Minnesota.

References

1. Goldstein JL, Brown MS (1990) Regulation of the mevalonate pathway. Nature 343:425–430
2. Lane KT, Beese LS (2006) Thematic review series: lipid post-translational modifications. Structural biology of protein farnesyltransferase and geranylgeranyltransferase type I. J Lipid Res 47:681–699
3. McTaggart SJ (2006) Isoprenylated proteins. Cell Mol Life Sci 63:255–267
4. 4S Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383–1389
5. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335:1001–1009
6. Brown MS, Goldstein JL (1986) A receptor-mediated pathway for cholesterol homeostasis. Science 232:34–47
7. Jones PH (2003) Comparing HMG-CoA reductase inhibitors. Clin Cardiol 26:I15–20
8. Shitara Y, Sugiyama Y (2006) Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. Pharmacol Ther 112:71–105
9. Istvan ES, Deisenhofer J (2001) Structural mechanism for statin inhibition of HMG-CoA reductase. Science 292:1160–1164
10. Schachter M (2005) Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol 19:117–125
11. Yee LL, Wright EA (2011) Pitavastatin calcium: clinical review of a new antihyperlipidemic medication. Clin Ther 33:1023–1042
12. Liao JK (2002) Isoprenoids as mediators of the biological effects of statins. J Clin Invest 110:285–288
13. Vaughan CJ (2003) Prevention of stroke and dementia with statins: effects beyond lipid lowering. Am J Cardiol 91:23B–29B
14. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H (2000) HMG-CoA reductase inhibitors and the risk of fractures. JAMA 283:3205–3210
15. Vollmer T, Key L, Durkalski V, Tyor W, Corboy J, Markovic-Plese S, Preiningerova J, Rizzo M, Singh I (2004) Oral simvastatin treatment in relapsing-remitting multiple sclerosis. Lancet 363:1607–1608
16. Shepardson NE, Shankar GM, Selkoe DJ (2010) Cholesterol level and statin use in Alzheimer disease: II. review of human trials and recommendations. Arch Neurol 68:1385–1392
17. Fernandez Martinez M, Castro Flores J, de Las P, Heras S, Mandaluniz Lekumberri A, Gordejuela Menocal M, Zarranz Imirizaldu JJ (2008) Risk factors for dementia in the epidemiological study of Munguialde County (Basque Country-Spain). BMC Neurol 8:39
18. Jarvik GP, Wijsman EM, Kukull WA, Schellenberg GD, Yu C, Larson EB (1995) Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: a case–control study. Neurology 45:1092–1096
19. Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, Girones X, Henry TL, Matsubara E, Zambon D, Wolozin B, Sano M, Cruz-Sanchez FF, Thal LJ, Petanceska SS, Refolo LM (2003) Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. Neurology 61:199–205
20. Fassbender K, Simons M, Bergmann C, Stroick M, Lutjohann D, Keller P, Runz H, Kuhl S, Bertsch T, von Bergmann K, Hennerici M, Beyreuther K, Hartmann T (2001) Simvastatin strongly reduces levels of Alzheimer's disease beta-amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. Proc Natl Acad Sci USA 98:5856–5861
21. Kojro E, Gimpl G, Lammich S, Marz W, Fahrenholz F (2001) Low cholesterol stimulates the nonamyloidogenic pathway by its effect on the alpha -secretase ADAM 10. Proc Natl Acad Sci USA 98:5815–5820
22. Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG, Simons K (1998) Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc Natl Acad Sci USA 95:6460–6464
23. Thinakaran G, Koo EH (2008) Amyloid precursor protein trafficking, processing, and function. J Biol Chem 283:29615–29619
24. Pedrini S, Carter TL, Prendergast G, Petanceska S, Ehrlich ME, Gandy S (2005) Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK. PLoS Med 2:e18
25. Cole SL, Grudzien A, Manhart IO, Kelly BL, Oakley H, Vassar R (2005) Statins cause intracellular accumulation of amyloid precursor protein, beta-secretase-cleaved fragments, and amyloid beta-peptide via an isoprenoid-dependent mechanism. J Biol Chem 280:18755–18770
26. Ostrowski SM, Wilkinson BL, Golde TE, Landreth G (2007) Statins reduce amyloid-beta production through inhibition of protein isoprenylation. J Biol Chem 282:26832–26844
27. Zhou Y, Suram A, Venugopal C, Prakasam A, Lin S, Su Y, Li B, Paul SM, Sambamurti K (2008) Geranylgeranyl pyrophosphate stimulates gamma-secretase to increase the generation of Abeta and APP-CTFgamma. FASEB J 22:47–54
28. Hooff GP, Peters I, Wood WG, Muller WE, Eckert GP (2010) Modulation of cholesterol, farnesylpyrophosphate, and geranylgeranylpyrophosphate in neuroblastoma SH-SY5Y-APP695 cells: impact on amyloid beta-protein production. Mol Neurobiol 41:341–350
29. Wolozin B, Manger J, Bryant R, Cordy J, Green RC, McKee A (2006) Re-assessing the relationship between cholesterol, statins and Alzheimer's disease. Acta Neurol Scand Suppl 185:63–70
30. Li L, Cao D, Kim H, Lester R, Fukuchi K (2006) Simvastatin enhances learning and memory independent of amyloid load in mice. Ann Neurol 60:729–739
31. Shinohara M, Sato N, Kurinami H, Takeuchi D, Takeda S, Shimamura M, Yamashita T, Uchiyama Y, Rakugi H, Morishita R

(2010) Reduction of brain beta-amyloid (Abeta) by fluvastatin, a hydroxymethylglutaryl-CoA reductase inhibitor, through increase in degradation of amyloid precursor protein C-terminal fragments (APP-CTFs) and Abeta clearance. J Biol Chem 285:22091–22102
32. Eikelenboom P, Veerhuis R, Exel EV, Hoozemans JJ, Rozemuller AJ, van Gool WA (2011) The early involvement of the innate immunity in the pathogenesis of late-onset Alzheimer's disease: neuropathological, epidemiological and genetic evidence. Curr Alzheimer Res 8:142–150
33. Abraham CR, Selkoe DJ, Potter H (1988) Immunochemical identification of the serine protease inhibitor alpha 1-antichymotrypsin in the brain amyloid deposits of Alzheimer's disease. Cell 52:487–501
34. Bauer J, Strauss S, Schreiter-Gasser U, Ganter U, Schlegel P, Witt I, Yolk B, Berger M (1991) Interleukin-6 and alpha-2-macroglobulin indicate an acute-phase state in Alzheimer's disease cortices. FEBS Lett 285:111–114
35. Coria F, Castano E, Prelli F, Larrondo-Lillo M, van Duinen S, Shelanski ML, Frangione B (1988) Isolation and characterization of amyloid P component from Alzheimer's disease and other types of cerebral amyloidosis. Lab Invest 58:454–458
36. Eikelenboom P, Stam FC (1982) Immunoglobulins and complement factors in senile plaques. An immunoperoxidase study. Acta Neuropathol 57:239–242
37. Cameron B, Landreth GE (2010) Inflammation, microglia, and Alzheimer's disease. Neurobiol Dis 37:503–509
38. Fuller S, Steele M, Munch G (2010) Activated astroglia during chronic inflammation in Alzheimer's disease–do they neglect their neurosupportive roles? Mutat Res 690:40–49
39. Morgan K (2011) The three new pathways leading to Alzheimer's disease. Neuropathol Appl Neurobiol 37:353–357
40. Menge T, Hartung HP, Stuve O (2005) Statins–a cure-all for the brain? Nat Rev Neurosci 6:325–331
41. Sun YX, Crisby M, Lindgren S, Janciauskiene S (2003) Pravastatin inhibits pro-inflammatory effects of Alzheimer's peptide Abeta(1-42) in glioma cell culture in vitro. Pharmacol Res 47:119–126
42. Wang H, Lynch JR, Song P, Yang HJ, Yates RB, Mace B, Warner DS, Guyton JR, Laskowitz DT (2007) Simvastatin and atorvastatin improve behavioral outcome, reduce hippocampal degeneration, and improve cerebral blood flow after experimental traumatic brain injury. Exp Neurol 206(1):59–69
43. Townsend KP, Shytle DR, Bai Y, San N, Zeng J, Freeman M, Mori T, Fernandez F, Morgan D, Sanberg P, Tan J (2004) Lovastatin modulation of microglial activation via suppression of functional CD40 expression. J Neurosci Res 78:167–176
44. Pahan K, Sheikh FG, Namboodiri AM, Singh I (1997) Lovastatin and phenylacetate inhibit the induction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia, and macrophages. J Clin Invest 100:2671–2679
45. Paintlia AS, Paintlia MK, Singh AK, Singh I (2008) Inhibition of rho family functions by lovastatin promotes myelin repair in ameliorating experimental autoimmune encephalomyelitis. Mol Pharmacol 73:1381–1393
46. Lindberg C, Crisby M, Winblad B, Schultzberg M (2005) Effects of statins on microglia. J Neurosci Res 82:10–19
47. Kou J, Kim HD, Jin J, Cao D, Li L, Lalonde R, Fukuchi K (2010) Simvastatin enhances immune responses to Abeta vaccination and attenuates vaccination-induced behavioral alterations. Brain Res 1356:102–111
48. Cordle A, Koenigsknecht-Talboo J, Wilkinson B, Limpert A, Landreth G (2005) Mechanisms of statin-mediated inhibition of small G-protein function. J Biol Chem 280:34202–34209
49. Cordle A, Landreth G (2005) 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors attenuate beta-amyloid-induced microglial inflammatory responses. J Neurosci 25:299–307
50. Franke C, Noldner M, Abdel-Kader R, Johnson-Anuna LN, Gibson Wood W, Muller WE, Eckert GP (2007) Bcl-2 upregulation and neuroprotection in guinea pig brain following chronic simvastatin treatment. Neurobiol Dis 25:438–445
51. Johnson-Anuna LN, Eckert GP, Keller JH, Igbavboa U, Franke C, Fechner T, Schubert-Zsilavecz M, Karas M, Muller WE, Wood WG (2005) Chronic administration of statins alters multiple gene expression patterns in mouse cerebral cortex. J Pharmacol Exp Ther 312:786–793
52. Famer D, Crisby M (2004) Rosuvastatin reduces caspase-3 activity and up-regulates alpha-secretase in human neuroblastoma SH-SY5Y cells exposed to A beta. Neurosci Lett 371:209–214
53. Zacco A, Togo J, Spence K, Ellis A, Lloyd D, Furlong S, Piser T (2003) 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors protect cortical neurons from excitotoxicity. J Neurosci 23:11104–11111
54. Bosel J, Gandor F, Harms C, Synowitz M, Harms U, Djoufack PC, Megow D, Dirnagl U, Hortnagl H, Fink KB, Endres M (2005) Neuroprotective effects of atorvastatin against glutamate-induced excitotoxicity in primary cortical neurones. J Neurochem 92:1386–1398
55. Lapchak PA, Han MK (2010) Simvastatin improves clinical scores in a rabbit multiple infarct ischemic stroke model: synergism with a ROCK inhibitor but not the thrombolytic tissue plasminogen activator. Brain Res 1344:217–225
56. Ghosh A, Roy A, Matras J, Brahmachari S, Gendelman HE, Pahan K (2009) Simvastatin inhibits the activation of p21ras and prevents the loss of dopaminergic neurons in a mouse model of Parkinson's disease. J Neurosci 29:13543–13556
57. Meske V, Albert F, Richter D, Schwarze J, Ohm TG (2003) Blockade of HMG-CoA reductase activity causes changes in microtubule-stabilizing protein tau via suppression of geranylgeranylpyrophosphate formation: implications for Alzheimer's disease. Eur J Neurosci 17:93–102
58. Ramirez C, Tercero I, Pineda A, Burgos JS (2011) Simvastatin is the statin that most efficiently protects against kainate-induced excitotoxicity and memory impairment. J Alzheimers Dis 24:161–174
59. Salins P, Shawesh S, He Y, Dibrov A, Kashour T, Arthur G, Amara F (2007) Lovastatin protects human neurons against Abeta-induced toxicity and causes activation of beta-catenin-TCF/LEF signaling. Neurosci Lett 412:211–216
60. Cespedes-Rubio A, Jurado FW, Cardona-Gomez GP (2010) p120 catenin/alphaN-catenin are molecular targets in the neuroprotection and neuronal plasticity mediated by atorvastatin after focal cerebral ischemia. J Neurosci Res 88:3621–3634
61. Kretz A, Schmeer C, Tausch S, Isenmann S (2006) Simvastatin promotes heat shock protein 27 expression and Akt activation in the rat retina and protects axotomized retinal ganglion cells in vivo. Neurobiol Dis 21:421–430
62. Xu R, Chen J, Cong X, Hu S, Chen X (2008) Lovastatin protects mesenchymal stem cells against hypoxia- and serum deprivation-induced apoptosis by activation of PI3K/Akt and ERK1/2. J Cell Biochem 103:256–269
63. Rodriguez-Vita J, Sanchez-Galan E, Santamaria B, Sanchez-Lopez E, Rodrigues-Diez R, Blanco-Colio LM, Egido J, Ortiz A, Ruiz-Ortega M (2008) Essential role of TGF-beta/Smad pathway on statin dependent vascular smooth muscle cell regulation. PLoS One 3:e3959
64. Balduini W, Mazzoni E, Carloni S, De Simoni MG, Perego C, Sironi L, Cimino M (2003) Prophylactic but not delayed administration of simvastatin protects against long-lasting cognitive and morphological consequences of neonatal hypoxic-ischemic brain injury, reduces interleukin-1beta and tumor necrosis factor-alpha mRNA induction, and does not affect endothelial nitric oxide synthase expression. Stroke 34:2007–2012

65. Chen J, Zhang ZG, Li Y, Wang Y, Wang L, Jiang H, Zhang C, Lu M, Katakowski M, Feldkamp CS, Chopp M (2003) Statins induce angiogenesis, neurogenesis, and synaptogenesis after stroke. Ann Neurol 53:743–751
66. Lu D, Qu C, Goussev A, Jiang H, Lu C, Schallert T, Mahmood A, Chen J, Li Y, Chopp M (2007) Statins increase neurogenesis in the dentate gyrus, reduce delayed neuronal death in the hippocampal CA3 region, and improve spatial learning in rat after traumatic brain injury. J Neurotrauma 24:1132–1146
67. Wu H, Lu D, Jiang H, Xiong Y, Qu C, Li B, Mahmood A, Zhou D, Chopp M (2008) Simvastatin-mediated upregulation of VEGF and BDNF, activation of the PI3K/Akt pathway, and increase of neurogenesis are associated with therapeutic improvement after traumatic brain injury. J Neurotrauma 25:130–139
68. Pooler AM, Xi SC, Wurtman RJ (2006) The 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitor pravastatin enhances neurite outgrowth in hippocampal neurons. J Neurochem 97:716–723
69. Kannan M, Steinert JR, Forsythe ID, Smith AG, Chernova T (2010) Mevastatin accelerates loss of synaptic proteins and neurite degeneration in aging cortical neurons in a heme-independent manner. Neurobiol Aging 31:1543–1553
70. Schulz JG, Bosel J, Stoeckel M, Megow D, Dirnagl U, Endres M (2004) HMG-CoA reductase inhibition causes neurite loss by interfering with geranylgeranylpyrophosphate synthesis. J Neurochem 89:24–32
71. Vural K, Tuglu MI (2011) Neurotoxic effect of statins on mouse neuroblastoma NB2a cell line. Eur Rev Med Pharmacol Sci 15:985–991
72. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA (2000) Statins and the risk of dementia. Lancet 356:1627–1631
73. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G (2000) Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3- methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 57:1439–1443
74. Simons M, Schwarzler F, Lutjohann D, von Bergmann K, Beyreuther K, Dichgans J, Wormstall H, Hartmann T, Schulz JB (2002) Treatment with simvastatin in normocholesterolemic patients with Alzheimer's disease: a 26-week randomized, placebo-controlled, double- blind trial. Ann Neurol 52:346–350
75. Sparks DL, Sabbagh MN, Connor DJ, Lopez J, Launer LJ, Browne P, Wasser D, Johnson-Traver S, Lochhead J, Ziolwolski C (2005) Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. Arch Neurol 62:753–757
76. Collins R, Armitage J, Parish S, Sleight P, Peto R (2002) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360:7–22
77. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG (2002) Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 360:1623–1630
78. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM (2003) Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 23:871–880
79. Shepardson NE, Shankar GM, Selkoe DJ (2010) Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. Arch Neurol 68:1239–1244
80. Douma TN, Borre Y, Hendriksen H, Olivier B, Oosting RS (2011) Simvastatin improves learning and memory in control but not in olfactory bulbectomized rats. Psychopharmacology (Berl) 216:537–544
81. McGaugh JL (2000) Memory—a century of consolidation. Science 287:248–251
82. Selkoe DJ (2002) Alzheimer's disease is a synaptic failure. Science 298:789–791
83. Clarke RM, O'Connell F, Lyons A, Lynch MA (2007) The HMG-CoA reductase inhibitor, atorvastatin, attenuates the effects of acute administration of amyloid-beta1-42 in the rat hippocampus in vivo. Neuropharmacology 52:136–145
84. Kotti TJ, Ramirez DM, Pfeiffer BE, Huber KM, Russell DW (2006) Brain cholesterol turnover required for geranylgeraniol production and learning in mice. Proc Natl Acad Sci USA 103:3869–3874
85. Kotti T, Head DD, McKenna CE, Russell DW (2008) Biphasic requirement for geranylgeraniol in hippocampal long-term potentiation. Proc Natl Acad Sci USA 105:11394–11399
86. Mans RA, Chowdhury N, Cao D, McMahon LL, Li L (2010) Simvastatin enhances hippocampal long-term potentiation in C57BL/6 mice. Neuroscience 166:435–444
87. Mans RA, McMahon LL, Li L (2011) Simvastatin-mediated enhancement of long-term potentiation is driven by farnesylpyrophosphate depletion and inhibition of farnesylation. Neuroscience. doi:10.1016/j.neuroscience.2011.12.007
88. Horwood JM, Dufour F, Laroche S, Davis S (2006) Signalling mechanisms mediated by the phosphoinositide 3-kinase/Akt cascade in synaptic plasticity and memory in the rat. Eur J Neurosci 23:3375–3384
89. Li W, Cui Y, Kushner SA, Brown RA, Jentsch JD, Frankland PW, Cannon TD, Silva AJ (2005) The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. Curr Biol 15:1961–1967
90. Thornton C, Yaka R, Dinh S, Ron D (2003) H-Ras modulates N-methyl-D-aspartate receptor function via inhibition of Src tyrosine kinase activity. J Biol Chem 278:23823–23829
91. Yaka R, Thornton C, Vagts AJ, Phamluong K, Bonci A, Ron D (2002) NMDA receptor function is regulated by the inhibitory scaffolding protein, RACK1. Proc Natl Acad Sci USA 99:5710–5715
92. Manabe T, Aiba A, Yamada A, Ichise T, Sakagami H, Kondo H, Katsuki M (2000) Regulation of long-term potentiation by H-Ras through NMDA receptor phosphorylation. J Neurosci 20:2504–2511
93. Eckert GP, Hooff GP, Strandjord DM, Igbavboa U, Volmer DA, Muller WE, Wood WG (2009) Regulation of the brain isoprenoids farnesyl- and geranylgeranylpyrophosphate is altered in male Alzheimer patients. Neurobiol Dis 35:251–257
94. Fleisch H, Russell RG, Straumann F (1966) Effect of pyrophosphate on hydroxyapatite and its implications in calcium homeostasis. Nature 212:901–903
95. Fleisch H, Russell RG, Francis MD (1969) Diphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo. Science 165:1262–1264
96. Fleisch H, Russell RG, Simpson B, Muhlbauer RC (1969) Prevention by a diphosphonate of immobilization "osteoporosis" in rats. Nature 223:211–212
97. Russell RG (2011) Bisphosphonates: the first 40 years. Bone 49:2–19
98. Rogers MJ, Crockett JC, Coxon FP, Monkkonen J (2011) Biochemical and molecular mechanisms of action of bisphosphonates. Bone 49:34–41
99. Roelofs AJ, Thompson K, Ebetino FH, Rogers MJ, Coxon FP (2010) Bisphosphonates: molecular mechanisms of action and effects on bone cells, monocytes and macrophages. Curr Pharm Des 16:2950–2960
100. Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, Wesolowski G, Russell RG, Rodan GA, Reszka AA (1999) Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of

osteoclast formation, bone resorption, and kinase activation in vitro. Proc Natl Acad Sci USA 96:133–138
101. Coxon FP, Helfrich MH, Van't Hof R, Sebti S, Ralston SH, Hamilton A, Rogers MJ (2000) Protein geranylgeranylation is required for osteoclast formation, function, and survival: inhibition by bisphosphonates and GGTI-298. J Bone Miner Res 15:1467–1476
102. Clezardin P, Ebetino FH, Fournier PG (2005) Bisphosphonates and cancer-induced bone disease: beyond their antiresorptive activity. Cancer Res 65:4971–4974
103. Dechat T, Shimi T, Adam SA, Rusinol AE, Andres DA, Spielmann HP, Sinensky MS, Goldman RD (2007) Alterations in mitosis and cell cycle progression caused by a mutant lamin A known to accelerate human aging. Proc Natl Acad Sci USA 104:4955–4960
104. Young SG, Meta M, Yang SH, Fong LG (2006) Prelamin A farnesylation and progeroid syndromes. J Biol Chem 281:39741–39745
105. Varela I, Pereira S, Ugalde AP, Navarro CL, Suarez MF, Cau P, Cadinanos J, Osorio FG, Foray N, Cobo J, de Carlos F, Levy N, Freije JM, Lopez-Otin C (2008) Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. Nat Med 14:767–772
106. Fawcett JR, Bordayo EZ, Jackson K, Liu H, Peterson J, Svitak A, Frey WH 2nd (2002) Inactivation of the human brain muscarinic acetylcholine receptor by oxidative damage catalyzed by a low molecular weight endogenous inhibitor from Alzheimer's brain is prevented by pyrophosphate analogs, bioflavonoids and other antioxidants. Brain Res 950:10–20
107. Cibickova L, Palicka V, Cibicek N, Cermakova E, Micuda S, Bartosova L, Jun D (2007) Differential effects of statins and alendronate on cholinesterases in serum and brain of rats. Physiol Res 56:765–770
108. Kavanagh KL, Guo K, Dunford JE, Wu X, Knapp S, Ebetino FH, Rogers MJ, Russell RG, Oppermann U (2006) The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. Proc Natl Acad Sci USA 103:7829–7834
109. Luckman SP, Coxon FP, Ebetino FH, Russell RG, Rogers MJ (1998) Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by preventing protein prenylation: evidence from structure-activity relationships in J774 macrophages. J Bone Miner Res 13:1668–1678
110. Rondeau JM, Bitsch F, Bourgier E, Geiser M, Hemmig R, Kroemer M, Lehmann S, Ramage P, Rieffel S, Strauss A, Green JR, Jahnke W (2006) Structural basis for the exceptional in vivo efficacy of bisphosphonate drugs. ChemMedChem 1:267–273
111. Jahnke W, Rondeau JM, Cotesta S, Marzinzik A, Pelle X, Geiser M, Strauss A, Gotte M, Bitsch F, Hemmig R, Henry C, Lehmann S, Glickman JF, Roddy TP, Stout SJ, Green JR (2010) Allosteric non-bisphosphonate FPPS inhibitors identified by fragment-based discovery. Nat Chem Biol 6:660–666
112. Leung KF, Baron R, Seabra MC (2006) Thematic review series: lipid posttranslational modifications. geranylgeranylation of Rab GTPases. J Lipid Res 47:467–475
113. Berndt N, Hamilton AD, Sebti SM (2011) Targeting protein prenylation for cancer therapy. Nat Rev Cancer 11:775–791
114. Tsimberidou AM, Chandhasin C, Kurzrock R (2010) Farnesyltransferase inhibitors: where are we now? Expert Opin Investig Drugs 19:1569–1580
115. Kohl NE, Mosser SD, deSolms SJ, Giuliani EA, Pompliano DL, Graham SL, Smith RL, Scolnick EM, Oliff A, Gibbs JB (1993) Selective inhibition of ras-dependent transformation by a farnesyltransferase inhibitor. Science 260:1934–1937
116. Liu M, Sjogren AK, Karlsson C, Ibrahim MX, Andersson KM, Olofsson FJ, Wahlstrom AM, Dalin M, Yu H, Chen Z, Yang SH, Young SG, Bergo MO (2010) Targeting the protein prenyltransferases efficiently reduces tumor development in mice with K-RAS-induced lung cancer. Proc Natl Acad Sci USA 107:6471–6476
117. Crespo NC, Ohkanda J, Yen TJ, Hamilton AD, Sebti SM (2001) The farnesyltransferase inhibitor, FTI-2153, blocks bipolar spindle formation and chromosome alignment and causes prometaphase accumulation during mitosis of human lung cancer cells. J Biol Chem 276:16161–16167
118. Crespo NC, Delarue F, Ohkanda J, Carrico D, Hamilton AD, Sebti SM (2002) The farnesyltransferase inhibitor, FTI-2153, inhibits bipolar spindle formation during mitosis independently of transformation and Ras and p53 mutation status. Cell Death Differ 9:702–709
119. Barrington RE, Subler MA, Rands E, Omer CA, Miller PJ, Hundley JE, Koester SK, Troyer DA, Bearss DJ, Conner MW, Gibbs JB, Hamilton K, Koblan KS, Mosser SD, O'Neill TJ, Schaber MD, Senderak ET, Windle JJ, Oliff A, Kohl NE (1998) A farnesyltransferase inhibitor induces tumor regression in transgenic mice harboring multiple oncogenic mutations by mediating alterations in both cell cycle control and apoptosis. Mol Cell Biol 18:85–92
120. Zhang B, Prendergast GC, Fenton RG (2002) Farnesyltransferase inhibitors reverse Ras-mediated inhibition of Fas gene expression. Cancer Res 62:450–458
121. Reuveni H, Klein S, Levitzki A (2003) The inhibition of Ras farnesylation leads to an increase in p27Kip1 and G1 cell cycle arrest. Eur J Biochem 270:2759–2772
122. Cohen-Jonathan E, Evans SM, Koch CJ, Muschel RJ, McKenna WG, Wu J, Bernhard EJ (2001) The farnesyltransferase inhibitor L744,832 reduces hypoxia in tumors expressing activated H-ras. Cancer Res 61:2289–2293
123. Kim CK, Choi YK, Lee H, Ha KS, Won MH, Kwon YG, Kim YM (2010) The farnesyltransferase inhibitor LB42708 suppresses vascular endothelial growth factor-induced angiogenesis by inhibiting ras-dependent mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt signal pathways. Mol Pharmacol 78:142–150
124. Lerner EC, Zhang TT, Knowles DB, Qian Y, Hamilton AD, Sebti SM (1997) Inhibition of the prenylation of K-Ras, but not H- or N-Ras, is highly resistant to CAAX peptidomimetics and requires both a farnesyltransferase and a geranylgeranyltransferase I inhibitor in human tumor cell lines. Oncogene 15:1283–1288
125. Rowell CA, Kowalczyk JJ, Lewis MD, Garcia AM (1997) Direct demonstration of geranylgeranylation and farnesylation of Ki-Ras in vivo. J Biol Chem 272:14093–14097
126. Whyte DB, Kirschmeier P, Hockenberry TN, Nunez-Oliva I, James L, Catino JJ, Bishop WR, Pai JK (1997) K- and N-Ras are geranylgeranylated in cells treated with farnesyl protein transferase inhibitors. J Biol Chem 272:14459–14464
127. Mehta IS, Bridger JM, Kill IR (2010) Progeria, the nucleolus and farnesyltransferase inhibitors. Biochem Soc Trans 38:287–291
128. Fong LG, Frost D, Meta M, Qiao X, Yang SH, Coffinier C, Young SG (2006) A protein farnesyltransferase inhibitor ameliorates disease in a mouse model of progeria. Science 311:1621–1623
129. Yang SH, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, Majumdar S, Bergo MO, Young SG, Fong LG (2006) A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. J Clin Invest 116:2115–2121
130. Capell BC, Olive M, Erdos MR, Cao K, Faddah DA, Tavarez UL, Conneely KN, Qu X, San H, Ganesh SK, Chen X, Avallone H, Kolodgie FD, Virmani R, Nabel EG, Collins FS (2008) A farnesyltransferase inhibitor prevents both the onset and late progression of cardiovascular disease in a progeria mouse model. Proc Natl Acad Sci USA 105:15902–15907
131. Kieran MW, Gordon L, Kleinman M (2007) New approaches to progeria. Pediatrics 120:834–841

132. Work LM, McPhaden AR, Pyne NJ, Pyne S, Wadsworth RM, Wainwright CL (2001) Short-term local delivery of an inhibitor of Ras farnesyltransferase prevents neointima formation in vivo after porcine coronary balloon angioplasty. Circulation 104:1538–1543
133. Eastman RT, Buckner FS, Yokoyama K, Gelb MH, Van Voorhis WC (2006) Thematic review series: lipid posttranslational modifications. Fighting parasitic disease by blocking protein farnesylation. J Lipid Res 47:233–240
134. Carrico D, Ohkanda J, Kendrick H, Yokoyama K, Blaskovich MA, Bucher CJ, Buckner FS, Van Voorhis WC, Chakrabarti D, Croft SL, Gelb MH, Sebti SM, Hamilton AD (2004) In vitro and in vivo antimalarial activity of peptidomimetic protein farnesyltransferase inhibitors with improved membrane permeability. Bioorg Med Chem 12:6517–6526
135. Nallan L, Bauer KD, Bendale P, Rivas K, Yokoyama K, Horney CP, Pendyala PR, Floyd D, Lombardo LJ, Williams DK, Hamilton A, Sebti S, Windsor WT, Weber PC, Buckner FS, Chakrabarti D, Gelb MH, Van Voorhis WC (2005) Protein farnesyltransferase inhibitors exhibit potent antimalarial activity. J Med Chem 48:3704–3713
136. Bordier BB, Ohkanda J, Liu P, Lee SY, Salazar FH, Marion PL, Ohashi K, Meuse L, Kay MA, Casey JL, Sebti SM, Hamilton AD, Glenn JS (2003) In vivo antiviral efficacy of prenylation inhibitors against hepatitis delta virus. J Clin Invest 112:407–414
137. Ye X, Carew TJ (2010) Small G protein signaling in neuronal plasticity and memory formation: the specific role of ras family proteins. Neuron 68:340–361
138. Costa RM, Federov NB, Kogan JH, Murphy GG, Stern J, Ohno M, Kucherlapati R, Jacks T, Silva AJ (2002) Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. Nature 415:526–530
139. Liu Z, Meray RK, Grammatopoulos TN, Fredenburg RA, Cookson MR, Liu Y, Logan T, Lansbury PT Jr (2009) Membrane-associated farnesylated UCH-L1 promotes alpha-synuclein neurotoxicity and is a therapeutic target for Parkinson's disease. Proc Natl Acad Sci USA 106:4635–4640
140. O'Dwyer PJ, Gallagher M, Nguyen B, Waddell MJ, Chiorean EG (2010) Phase I accelerated dose-escalating safety and pharmacokinetic (PK) study of GGTI-2418, a novel geranylgeranyltransferase I inhibitor in patients with refractory solid tumors. Ann Oncol 21:ii42
141. Finder JD, Litz JL, Blaskovich MA, McGuire TF, Qian Y, Hamilton AD, Davies P, Sebti SM (1997) Inhibition of protein geranylgeranylation causes a superinduction of nitric-oxide synthase-2 by interleukin-1beta in vascular smooth muscle cells. J Biol Chem 272:13484–13488
142. Zuckerbraun BS, Barbato JE, Hamilton A, Sebti S, Tzeng E (2005) Inhibition of geranylgeranyltransferase I decreases generation of vascular reactive oxygen species and increases vascular nitric oxide production. J Surg Res 124:256–263
143. Holmberg E, Nordstrom T, Gross M, Kluge B, Zhang SX, Doolen S (2006) Simvastatin promotes neurite outgrowth in the presence of inhibitory molecules found in central nervous system injury. J Neurotrauma 23:1366–1378
144. Reid TS, Terry KL, Casey PJ, Beese LS (2004) Crystallographic analysis of CaaX prenyltransferases complexed with substrates defines rules of protein substrate selectivity. J Mol Biol 343:417–433
145. Govek EE, Hatten ME, Van Aelst L (2011) The role of Rho GTPase proteins in CNS neuronal migration. Dev Neurobiol 71:528–553
146. Tolias KF, Duman JG, Um K (2011) Control of synapse development and plasticity by Rho GTPase regulatory proteins. Prog Neurobiol 94:133–148
147. Newey SE, Velamoor V, Govek EE, Van Aelst L (2005) Rho GTPases, dendritic structure, and mental retardation. J Neurobiol 64:58–74
148. Perez-Sala D (2007) Protein isoprenylation in biology and disease: general overview and perspectives from studies with genetically engineered animals. Front Biosci 12:4456–4472
149. Maurer-Stroh S, Koranda M, Benetka W, Schneider G, Sirota FL, Eisenhaber F (2007) Towards complete sets of farnesylated and geranylgeranylated proteins. PLoS Comput Biol 3:e66
150. Chan LN, Hart C, Guo L, Nyberg T, Davies BS, Fong LG, Young SG, Agnew BJ, Tamanoi F (2009) A novel approach to tag and identify geranylgeranylated proteins. Electrophoresis 30:3598–3606
151. DeGraw AJ, Palsuledesai C, Ochocki JD, Dozier JK, Lenevich S, Rashidian M, Distefano MD (2010) Evaluation of alkyne-modified isoprenoids as chemical reporters of protein prenylation. Chem Biol Drug Des 76:460–471
152. Kho Y, Kim SC, Jiang C, Barma D, Kwon SW, Cheng J, Jaunbergs J, Weinbaum C, Tamanoi F, Falck J, Zhao Y (2004) A tagging-via-substrate technology for detection and proteomics of farnesylated proteins. Proc Natl Acad Sci USA 101:12479–12484
153. Nguyen UT, Guo Z, Delon C, Wu Y, Deraeve C, Franzel B, Bon RS, Blankenfeldt W, Goody RS, Waldmann H, Wolters D, Alexandrov K (2009) Analysis of the eukaryotic prenylome by isoprenoid affinity tagging. Nat Chem Biol 5:227–235
154. Onono FO, Morgan MA, Spielmann HP, Andres DA, Subramanian T, Ganser A, Reuter CW (2010) A tagging-via-substrate approach to detect the farnesylated proteome using two-dimensional electrophoresis coupled with Western blotting. Mol Cell Proteomics 9:742–751
155. Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, Ebetino FH, Rogers MJ (2001) Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. J Pharmacol Exp Ther 296:235–242
156. Leu CT, Luegmayr E, Freedman LP, Rodan GA, Reszka AA (2006) Relative binding affinities of bisphosphonates for human bone and relationship to antiresorptive efficacy. Bone 38:628–636
157. Cremers S, Papapoulos S (2011) Pharmacology of bisphosphonates. Bone 49:42–49
158. Essig M, Nguyen G, Prie D, Escoubet B, Sraer JD, Friedlander G (1998) 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors increase fibrinolytic activity in rat aortic endothelial cells. Role of geranylgeranylation and Rho proteins. Circ Res 83:683–690
159. Lin CH, Yeh SH, Lu KT, Leu TH, Chang WC, Gean PW (2001) A role for the PI-3 kinase signaling pathway in fear conditioning and synaptic plasticity in the amygdala. Neuron 31:841–851
160. Magrane J, Rosen KM, Smith RC, Walsh K, Gouras GK, Querfurth HW (2005) Intraneuronal beta-amyloid expression downregulates the Akt survival pathway and blunts the stress response. J Neurosci 25:10960–10969
161. O'Dell TJ, Huang PL, Dawson TM, Dinerman JL, Snyder SH, Kandel ER, Fishman MC (1994) Endothelial NOS and the blockade of LTP by NOS inhibitors in mice lacking neuronal NOS. Science 265:542–546
162. Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S, Teng KK, Yung WH, Hempstead BL, Lu B (2004) Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 306:487–491
163. Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P (2005) Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci 8:1051–1058
164. Sweatt JD (2004) Mitogen-activated protein kinases in synaptic plasticity and memory. Curr Opin Neurobiol 14:311–317