

# SC75741 Enhances TFEB Activity and Suppresses NF-κB: A Novel Strategy Against Protein Aggregation Disorders and Sterile Inflammation

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**Introduction**

By 2050 the population aged 65 will exceed 1.5 billion and the aging population in economically advanced countries will be an increasing medical and economical problem of great proportion therefore gerontological protective or anti-aging medicines are of great importance in todays and future societies. Long considered a topic for dietary supplements and not taken seriously by hard core drug research, it came into focus of evidence-based drug discovery research and is now well established in biomedical research. I would like to describe my experience from the perspective of a retired and therefore concerned party on this topic. Aging is accompanied by serious health problems like cardiovascular, hyperproliferative or cognitive decline problems. While great improvements of drugs to treat cardiovascular diseases have been achieved, the field of anticancer drugs is still in progress and a large percentage of health problems in the aging population concern neurodegenerative disorders like Parkinson's Disease, Dementia with Lewy Bodies, Multiple System Atrophy, and Pure Autonomic failure and the multiple forms of Neuropathies Du N, et al. [1,2]. Alzheimer's disease is a multifaceted neurodegenerative condition that cannot be attributed to a single cause but rather arises from the interplay of several biological mechanisms. Fundamentally, it is marked by abnormal buildup of amyloid beta plaques and tau tangles in the brain, disrupting neuron communication and causing cell death.

However, this protein aggregation is influenced by genetic and metabolic factors, most notably the presence of the APOE4 allele. APOE4 is a variant of the apolipoprotein E gene that significantly increases the risk of late-onset Alzheimer's by impairing the clearance of amyloid beta and promoting tau pathology. Beyond genetics, lipid dysregulation plays a crucial role in disease's progression. The brain relies heavily on lipid metabolism for maintaining cell membrane integrity, synaptic function, and myelin production. Disruptions in cholesterol and other lipid pathways which are often exacerbated by APOE4 and can lead to increased amyloid deposition, a heightened tau phosphorylation, and chronic neuroinflammation. Thus, Alzheimer's is best understood as a disease caused by abnormal protein aggregation driven dysfunction, that ultimately lead to cognitive decline. Harris G A, et al. [3]. Age related protein deposits like alpha-synuclein aggregation of misfolded alpha-synuclein aggregates into toxic oligomers and fibrils disrupting neuronal function and causing cell death include Parkinson's Disease, Dementia with Lewy Bodies, Multiple System Atrophy, and Pure autonomic failure. Alpha-synuclein is a protein normally found in the presynaptic terminals of neurons. It plays a role in synaptic function and neurotransmitter release. In PD, alpha-synuclein misfolds and aggregates, forming Lewy bodies (LBs) and Lewy neurites. These are abnormal protein inclusions found in neurons and are considered pathological hallmarks of the disease.

Similarly, beta amyloid in Alzheimer's disease, beta-amyloid peptides accumulate abnormally in the brain, forming sticky extracellular plaques that disrupt neuronal communication and trigger a cascade of neurodegenerative processes including inflammation, synaptic dysfunction, and cell death. These plaques are a defining pathological hallmark of the disease, and therapies targeting A $\beta$  clearance have shown promise in slowing early-stage progression. Reddy PH, et al. [4]. Neuropathic pain, resulting from damage or dysfunction of the somatosensory system, is increasingly prevalent among the aging population, with estimates suggesting that up to 50% of adults older than 85 years old may be affected. Age-related anatomical and physiological changes, such as neuronal loss, altered neurotransmitter function, and diminished pain inhibition, contribute to both the underreporting and complexity of managing this condition in elderly individuals. Pharmacological treatment often involves gabapentin, particularly pregabalin and gabapentin, which modulate calcium channel activity to reduce excitatory neurotransmitter release. Comparative studies indicate that pregabalin may offer superior efficacy and tolerability over gabapentin, especially in reducing pain intensity and improving quality of life. Concurrently, aging is a major risk factor for neurodegenerative diseases characterized by abnormal aggregation of misfolded proteins such as amyloid- $\beta$ , tau, and  $\alpha$ -synuclein.

These aggregates disrupt protein homeostasis and propagate via prion-like mechanisms, contributing to neuronal dysfunction and degeneration. Understanding the interplay between chronic pain, pharmacological interventions, and protein homeostasis-related neurodegeneration is essential for developing comprehensive therapeutic strategies for the elderly. Liao MF, et al. [5,6]. Autophagy is a cellular process for clearing damaged proteins and organelles and plays a crucial role in Alzheimer's disease by removing toxic aggregates like amyloid-beta and tau. The mTOR pathway is a key regulator of autophagy, and its overactivation in Alzheimer inhibits this clearance mechanism. While mTOR inhibitors like rapamycin have shown promise in restoring autophagic function, C. Moussa at Georgetown University proposed that TDP-43 phosphorylation may be a contributing factor in aberrant protein homeostasis and that Tyrosine Kinase inhibitors can induce degradation of misfolded or toxic proteins in an mTOR independent mechanism. Vilchez D, et al. [7-9]. We used a computer-based screening method to find new non-peptic proteasome inhibitors and found a compound with a 200 nM inhibition in a reporter gen assay of the NF- $\kappa$ B pathway, later it was found to be multi-kinase inhibitor and it was further improved by medicinal chemistry, thus the compound SC75741 was found which inhibited NF- $\kappa$ B in a proteasome independent manner.

SC75741 N-(6-benzoyl-1H-benzo[d]imidazol-2-yl)-2-(1-(thieno[3,2-d] pyrimidin-4-yl) piperidin-4-yl) thiazole-4-carboxamide was a novel NF $\kappa$ B inhibitor which has shown to be active as antiviral, anti-inflammatory and anticancer agent. Because of its potent activity of inhibiting the NF- $\kappa$ B pathway this compound was used in many pub-

lications as a reference NF- $\kappa$ B inhibitor, and the compound is offered for sale by several companies. The compound was found to be an autophagy inducing molecules by the mode of inhibiting cAb1, which was in good agreement with the work of others on cAb1 inhibitors like Imatinib. Our work with this compound and a kinase screen indicated that the compound was a multi-kinase inhibitor and that this could be the mode of action of its autophagy inducing and anti-inflammatory activity. SC75741 has a relatively large MW and incorporates several pharmacophores which are present in other autophagy inducing molecules therefore a multi-mode of action may be possible. Leban J, et al. [10,11]. SC75741 showed immunosuppressive activity by inhibiting proliferation of human PBMC with an IC50 of 2.2  $\mu$ m. SC75741 Inhibits Influenza A and B by inhibiting the NF- $\kappa$ B-mediated signaling pathway at the transcriptional level Virus. In addition, SC75741 showed a high barrier effect on the development of antiviral variants. SC75741 showed immunosuppressive activity by inhibiting proliferation of human PBMC and Inhibits Influenza A and B by blocking the NF- $\kappa$ B-mediated signaling pathway at the transcriptional level Virus.

In addition, SC75741 showed a high barrier effect on the development of antiviral variants. After injection of H5N1 Virus, SC75741 (15 mg/kg, I. P.) reduced Virus replication and cytokine expression in the lungs of mice. Erhard C, et al. [12]. Evidence is increasing that aberrant NF- $\kappa$ B activation is crucial for multiple myeloma pathophysiology and a promising target for new antimyeloma therapies. In a study, we assessed the in vitro antimyeloma activity of the novel NF- $\kappa$ B inhibitor SC7541. The study examined how the drug moves through the body and its potential toxic effects in living organisms. In mice, plasma concentrations of 10  $\mu$ mol/L could be reached without relevant toxicity. At this concentration, the compound potently induced apoptosis in all four multiple myeloma cell lines assessed as well as in primary multiple myeloma cells. Apoptosis induced by V1810 was associated with proteasome independent inhibition of NF- $\kappa$ B signaling, downregulation of Mcl-1, and caspase 3 cleavage. When apoptosis was induced in OPM2, U266, and RPMI-8226 cells, it also led to a halt in their cell cycles. Western blots revealed downregulation of Cdk4 as well as cyclin D1 (U266) or cyclin D2 (OPM2, NCI-H929, RPMI-8226), but not cyclin D3. Retinoblastoma protein was consistently observed in a state of hyperphosphorylation. Furthermore, V1810 reverses NF- $\kappa$ B activation induced by the genotoxic drugs melphalan and doxorubicin. V1810 and melphalan synergistically decrease multiple myeloma cell viability.

Taken together, the novel, proteasome-independent NF- $\kappa$ B inhibitor SC75741 induced apoptosis and cell cycle arrest in multiple myeloma cells at a concentration range that can be achieved in vivo. Moreover, reverses NF- $\kappa$ B activation by alkylating drugs and overcome NF- $\kappa$ B-mediated resistance to melphalan. Meinel FG, et al. [13]. Another study suggests that RIPK2/NF- $\kappa$ B is a potential target for treating glioma stemness and that SC75741 can attenuate stemness and can counteract chemotherapy resistance and this may provide

theoretical support for clinical treatment. RIP2 mediates TMZ resistance by regulating the maintenance of stemness in glioma cells through NF- $\kappa$ B. Interventions targeting the RIP2/NF- $\kappa$ B pathway may be a new strategy for TMZ-resistant glioma. In vitro studies have also shown that RIP2 increases the levels of glioma stem cell marker proteins CD133 and SOX-2 via the NF- $\kappa$ B pathway. To further confirm the biological role of RIP2 in vivo, we used a xenograft tumor model. Researchers observed that U251 cell xenografts transfected with the RIP2 plasmid showed higher levels of CD133 and SOX-2 expression. Immunohistochemical staining showed that the expression of CD133 and SOX-2 in U251 tumor tissue transfected with RIP2 plasmid was significantly up-regulated. Afterwards, U251 cells with elevated levels of RIP2 were exposed to SC75741, which resulted in a decrease in CD133 and SOX-2 protein expression. Following this, a xenograft tumor model using U251 cells that overexpress RIP2 was established, and these xenografts showed reduced sensitivity to TMZ, with a T/C value of just 85.9%.

After treatment with SC75741, TMZ had better tumor-inhibitory effect in this model. Wang XL, et al. [14]. Prolonged activation of nuclear factor NF $\kappa$ B signaling significantly contributes to the development of colorectal cancer. New therapeutic opportunities are emerging from targeting this distorted cell signaling transduction. Here, we discovered the critical role of RING finger 138 (RNF138) in CRC tumorigenesis through regulating the NF- $\kappa$ B signaling, which is independent of its Ubiquitin-E3 ligase activity involved in DNA damage response. RNF138-/- mice were hyper-susceptible to the switch from colitis to aggressive malignancy, which coincided with sustained aberrant NF- $\kappa$ B signaling in the colonic cells. Furthermore, RNF138 suppresses the activation of NF $\kappa$ B signaling pathway through preventing the translocation of NIK and IKK-Beta Binding Protein (NIBP) to the cytoplasm, which requires the ubiquitin interaction motif domain. More importantly, we uncovered a significant correlation between poor prognosis and the downregulation of RNF138 associated with reinforced NF- $\kappa$ B signaling in clinical settings, raising the possibility of RNF138 dysregulation as an indicator for the therapeutic intervention targeting NF- $\kappa$ B signaling. Using the xenograft models built upon either RNF138-deficient CRC cells or the cells derived from the RNF138-dysregulated CRC patients, we demonstrated that the inhibition of NF- $\kappa$ B signaling effectively hampered tumor growth.

Overall, our work defined the pathogenic role of aberrant NF- $\kappa$ B signaling due to RNF138 downregulation in the cascade events from the colitis switch to colonic neoplastic transformation and progression and highlights the possibility of targeting the NF- $\kappa$ B signaling in treating specific subtypes of CRC indicated by RNF138-ablation. Lu Y, et al. [15]. SC75741 shows in a kinase inhibitor selectivity Ambit assay with several kinases which are involved in autophagy and autophagic flux such as cABL and several mutants of cABL, CSK1-delta, DDR1, KIT, RIPK2, TAOK, MYLK, RET, JNK3, CLK (J. Leban private information) in addition it has a pharmacophore like Albendazole and Flubendazole

Lin S, et al. [16], which may indicate a microtubule-related interaction. SC74741 was reported to inhibit soluble epoxide hydrolase in an enzyme assay in the nanomolar range. Hoffman D, et al. [17]. Discoidin Domain Receptor 1 kinase (DDR1) is a collagen-activated receptor tyrosine kinase that plays a key role in cellular processes such as adhesion, migration, and extracellular matrix remodeling. In the context of neurodegenerative diseases, DDR1 has emerged as a critical regulator of autophagy and overactivation of DDR1 has been associated with impaired autophagic flux, leading to the accumulation of toxic proteins like amyloid-beta and tau in neurons. Inhibiting DDR1, as shown in studies involving the leukemia drug nilotinib, restores autophagy by modulating autophagy-related genes, reducing neuroinflammation, and enhancing the clearance of pathological aggregates.

This makes DDR1 a promising therapeutic target for conditions such as Alzheimer's and Parkinson's disease, where defective autophagy contributes to disease progression. Pagan F, et al. [18]. KIT inhibition has emerged as a promising strategy not only for cancer therapy but also for broader applications in aging and neurodegenerative diseases. By blocking KIT signaling, which is often hyperactivated in certain malignancies, KIT inhibitors can induce apoptosis through mechanisms involving caspase activation and suppression of survival pathways like PI3K/Akt/mTOR. Interestingly, recent research suggests that KIT inhibitors may also have potential in anti-aging and Alzheimer's disease therapy. In Alzheimer's models, KIT-targeting compounds such as BK40143 and BK40197 have shown the ability to reduce neuroinflammation and promote autophagic clearance of toxic proteins like amyloid-beta and tau, leading to improved cognitive outcomes. These effects are likely mediated through modulation of microglial activity and enhancement of cellular stress responses, which are central to both aging and neurodegeneration. While the connection between KIT inhibition and systemic anti-aging effects is still under investigation, its role in promoting apoptosis of dysfunctional cells and reducing neuroinflammation positions as a compelling candidate for future therapeutic development in age-related diseases, including Alzheimer's. Stevenson M, et al. [19]. SC75741 has also been shown to stimulate autophagy in a mTOR independent manner.

A recent study determined that the accumulation of mutant TDP-43, which is found in ALS patients, can be reduced through SC75741. SC75741 inhibits c-Abl at around 300 nM, an oncogene and non-receptor tyrosine kinase. C-Abl has been shown to inhibit TFE2 nuclear translocation independent of mTORC1, and when inhibited,  $\alpha$ -synuclein aggregates are cleared. The study's authors found through immunoblotting that in p62 KO HEK293T cells, TDP-25 increased upon the administration of SC75741. SC75741 mediates an increase of p62 and LC3C (the mammalian equivalent of Atg5 in yeast) expression, resulting in a decrease in TDP-25. SC75741 enhanced the interaction between p62 with TDP25 and LC3C, thus promoting TDP25 degradation, these data indicate that compounds like SC75741 could be important leads toward new drugs targeting Alzheimer disease and

Parkinson diseases. Transcription Factor EB (TFEB) is a key regulator of cellular clearance and energy homeostasis. It belongs to the MiTF/TFE family and controls the expression of genes involved in lysosomal biogenesis and autophagy by binding to CLEAR (Coordinated Lysosomal Expression and Regulation) elements in DNA. Under normal conditions, TFEB is phosphorylated by mTORC1 and retained in the cytoplasm. During stress or nutrient deprivation, mTORC1 inhibition and other signals trigger TFEB dephosphorylation, allowing its nuclear translocation and activation of a transcriptional program that enhances lysosomal function and autophagic flux, thereby promoting cellular adaptation and survival.

Beyond its role in autophagy, TFEB influences lipid metabolism, mitochondrial quality control, and immune responses, making it relevant in health and disease. Dysregulation of TFEB activity has been linked to neurodegenerative disorders, lysosomal storage diseases, and cancer. For example, TFEB activation facilitates the clearance of toxic protein aggregates such as  $\alpha$ -synuclein in Parkinson's disease, offering therapeutic potential. Compounds like Rapamycin, Imatinib and SC75741 have been shown to upregulate TFEB activity, highlighting its importance as a drug target for conditions involving impaired cellular clearance. Zhou D, et al. [20]. SC75741 acts as a potent NF- $\kappa$ B inhibitor that disrupts the transcriptional activation of osteogenic genes. In valvular interstitial cells (VICs) exposed to osteogenic conditions, NF- $\kappa$ B normally binds to the Runx2 promoter, driving Runx2 expression and promoting pathological calcification. By blocking NF- $\kappa$ B's DNA-binding activity, SC75741 reduces Runx2 transcription, thereby attenuating the osteogenic signaling cascade and significantly ameliorating VIC calcification. This mechanism positions SC75741 as a promising therapeutic candidate for preventing calcific aortic valve disease through targeted inhibition of NF- $\kappa$ B-mediated osteogenic pathways. SC75741 is a small-molecule inhibitor of NF- $\kappa$ B signaling that interferes with its DNA-binding activity, thereby reducing transcription of NF- $\kappa$ B target genes, including SQSTM1/p62. Since p62 functions as a selective autophagy receptor and a scaffold for stress-response pathways, its downregulation by SC75741 can impair autophagic clearance of ubiquitinated proteins and disrupt Keap1-Nrf2 antioxidant signaling.

While NF- $\kappa$ B does not directly regulate Ubiquilin-2 (UBQLN2), UBQLN2 relies on working with p62 to transport misfolded proteins to degradation pathways. Consequently, SC75741 indirectly affects UBQLN2 by limiting p62-mediated autophagy, potentially overloading proteasomal routes and exacerbating aggregate accumulation in proteostasis-related disorders such as ALS and FTD. While this inhibition may reduce NF- $\kappa$ B-driven inflammation, it poses risks for conditions requiring robust protein quality control. Weng PW, et al. [21]. The NF- $\kappa$ B inhibitory activity of SC75741 is well established by over 200 literature references, the precise MOA is not fully established but seems to be linked to its multi-kinase inhibitory profile. SC75741's autophagy inducing property seems to be related to its inhibitory activity on c-ABL kinase as reported by Zhou D, et al. [20]. Another

Publication by Meng Zhang 2021 shows that mTORC1 is linked to the NF- $\kappa$ B pathway and that SC75741 inhibits MTORC1 via NF- $\kappa$ B. To verify the effects of NF- $\kappa$ B on the expression of catabolic amino acid pathways, SC75741, a specific inhibitor of NF- $\kappa$ B was used to inhibit NF- $\kappa$ B activation in HL-7702 cells and then measured the levels of metabolic gene expression and intracellular enzymes. Primary amino acid catabolic pathways include transamination, oxidative deamination, and decarboxylation, which are catalyzed by specific enzymes, including aspartate aminotransferase (AST), glutamate dehydrogenase (GDH), glutamic acid decarboxylase (GAD), and ornithine decarboxylase (ODC), in liver cells.

The results showed that NF- $\kappa$ B activation was inhibited by the SC75741 and the mRNA levels of AST, GDH, GAD, and ODC and the corresponding intracellular enzyme levels were significantly decreased following SC75741 treatment, suggesting that NF- $\kappa$ B may direct the expression of AST, GDH, GAD, and ODC. To verify that mTORC1 regulates the expression of AST, GDH, GAD, and ODC through NF- $\kappa$ B, Rheb-overexpressing HL-7702 cells were treated with 10  $\mu$ M SC75741 for 12 h, after which NF- $\kappa$ B phosphorylation and the expression levels of the amino acid catabolic genes were evaluated. The results showed that NF- $\kappa$ B activation was enhanced by Rheb overexpression and inhibited by SC75741, and the gene expression pattern was like a pattern observed for NF- $\kappa$ B phosphorylation. These results indicated that mTORC1 likely controls the expression of these catabolic genes via NF- $\kappa$ B in hepatocytes. Meng Zhang 2021. In summary, research with SC75741 highlights the Benzimidazole scaffold as a key structure in kinase inhibitor design, showing that specific substitutions strongly affect inhibitor specificity and our starting point of these inhibitors was the compound SC75741, and we published it as a NF- $\kappa$ B inhibitor with antiviral activity which had an impact as a reference NF- $\kappa$ B inhibitor when NF- $\kappa$ B is set in a larger context of biological pathways. However, newer data claim a more complex mode of action as it may induce autophagy in a neurodegeneration context and can inhibit stemness in a cancer context.

Autophagy inducing activity in Tyrosine kinase inhibitors is well known and the Tyrosine kinase inhibitory activity is also reported to induce autophagy. While NF- $\kappa$ B inhibitory activity can be linked to this profile and Tyrosine kinase inhibitors do indirectly inhibit NF- $\kappa$ B, I do not think that this is the sole mode of action of SC75741. Further SC75741 has been reported to inhibit soluble epoxide hydrolase (sEH) in an enzyme assay and in a kinase independent mode. Although our early mouse tumor models yielded limited results, recent studies suggest that SC75741 and its similar molecules could be beneficial primarily when combined with other drugs and be of benefit when targeting alkylating agent- resistant tumors. SC75741 represents a novel and promising therapeutic candidate for neurodegenerative diseases by combining mTOR-independent TFEB activation with c-Abl inhibition, thereby restoring autophagy and lysosomal function while promoting clearance of toxic protein aggregates. Importantly, its ability to inhibit NF- $\kappa$ B signaling adds an extra layer of benefit by reducing neuroin-

flammation, a key contributor to disease progression. This unique multi-target profile positions SC75741 as a superior alternative to traditional TFEB activators and underscores its potential for future clinical development in ALS, Parkinson's, Alzheimer's, and related disorders. Sterile chronic inflammation, driven by damage-associated molecular patterns (DAMPs) rather than pathogens, is a key contributor to tissue dysfunction and age-related diseases.

Central to this process is NF-κB, a transcription factor that orchestrates pro-inflammatory signaling and perpetuates the low-grade inflammation characteristic of "inflammaging." Emerging evidence highlights SC75741, a potent NF-κB inhibitor, as a promising candidate for mitigating sterile inflammation. By blocking NF-κB DNA-binding activity, SC75741 reduces cytokine expression and downstream inflammatory cascades, showing efficacy in preclinical models of osteoarthritis and hypercytokinemia. Although currently limited to experimental use, its ability to target a fundamental pathway of chronic inflammation positions SC75741 as a potential therapeutic strategy for age-associated disorders, warranting further investigation into its safety and translational potential and initiating further medicinal chemistry to fine tune the PK and provide a classical Toxicological profile Ahmad A, et al. [22-26].

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