

# UC Davis

## UC Davis Previously Published Works

### Title

FDA-Approved Kinase Inhibitors in Preclinical and Clinical Trials for Neurological Disorders

### Permalink

<https://escholarship.org/uc/item/2hw9b91f>

### Journal

Pharmaceuticals, 15(12)

### ISSN

1424-8247

### Authors

Lui, Austin

Vanleuven, Jordan

Perekopskiy, David

et al.

### Publication Date

2022

### DOI

10.3390/ph15121546


### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Review

# FDA-Approved Kinase Inhibitors in Preclinical and Clinical Trials for Neurological Disorders

Austin Lui <sup>1</sup>, Jordan Vanleuven <sup>1</sup>, David Perekopskiy <sup>1</sup>, Dewey Liu <sup>1</sup>, Desiree Xu <sup>1</sup>, Omar Alzayat <sup>1</sup>, Taiseer Elgokhy <sup>1</sup>, Timothy Do <sup>1</sup>, Meghan Gann <sup>1</sup>, Ryan Martin <sup>2</sup> and Da-Zhi Liu <sup>1,3,\*</sup>

<sup>1</sup> Department of Neurology, University of California at Davis, Davis, CA 95618, USA

<sup>2</sup> Department of Neurological Surgery and Neurology, University of California at Davis, Davis, CA 95618, USA

<sup>3</sup> Mirnova Therapeutics, Inc., Davis, CA 95618, USA

\* Correspondence: dzliu@ucdavis.edu; Tel.: +1-530-754-5004

**Abstract:** Cancers and neurological disorders are two major types of diseases. We previously developed a new concept termed “Aberrant Cell Cycle Diseases” (ACCD), revealing that these two diseases share a common mechanism of aberrant cell cycle re-entry. The aberrant cell cycle re-entry is manifested as kinase/oncogene activation and tumor suppressor inactivation, which are hallmarks of *both* tumor growth in cancers and neuronal death in neurological disorders. Therefore, some cancer therapies (e.g., kinase inhibition, tumor suppressor elevation) can be leveraged for neurological treatments. The United States Food and Drug Administration (US FDA) has so far approved 74 kinase inhibitors, with numerous other kinase inhibitors in clinical trials, mostly for the treatment of cancers. In contrast, there are dire unmet needs of FDA-approved drugs for neurological treatments, such as Alzheimer’s disease (AD), intracerebral hemorrhage (ICH), ischemic stroke (IS), traumatic brain injury (TBI), and others. In this review, we list these 74 FDA-approved kinase-targeted drugs and identify those that have been reported in preclinical and/or clinical trials for neurological disorders, with a purpose of discussing the feasibility and applicability of leveraging these cancer drugs (FDA-approved kinase inhibitors) for neurological treatments.

**Keywords:** aberrant cell cycle disease; cancers; neurological disorders; kinase inhibitors



**Citation:** Lui, A.; Vanleuven, J.; Perekopskiy, D.; Liu, D.; Xu, D.; Alzayat, O.; Elgokhy, T.; Do, T.; Gann, M.; Martin, R.; et al. FDA-Approved Kinase Inhibitors in Preclinical and Clinical Trials for Neurological Disorders. *Pharmaceuticals* **2022**, *15*, 1546. <https://doi.org/10.3390/ph15121546>

Academic Editor: Damian Holsinger

Received: 10 October 2022

Accepted: 9 December 2022

Published: 13 December 2022

**Publisher’s Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



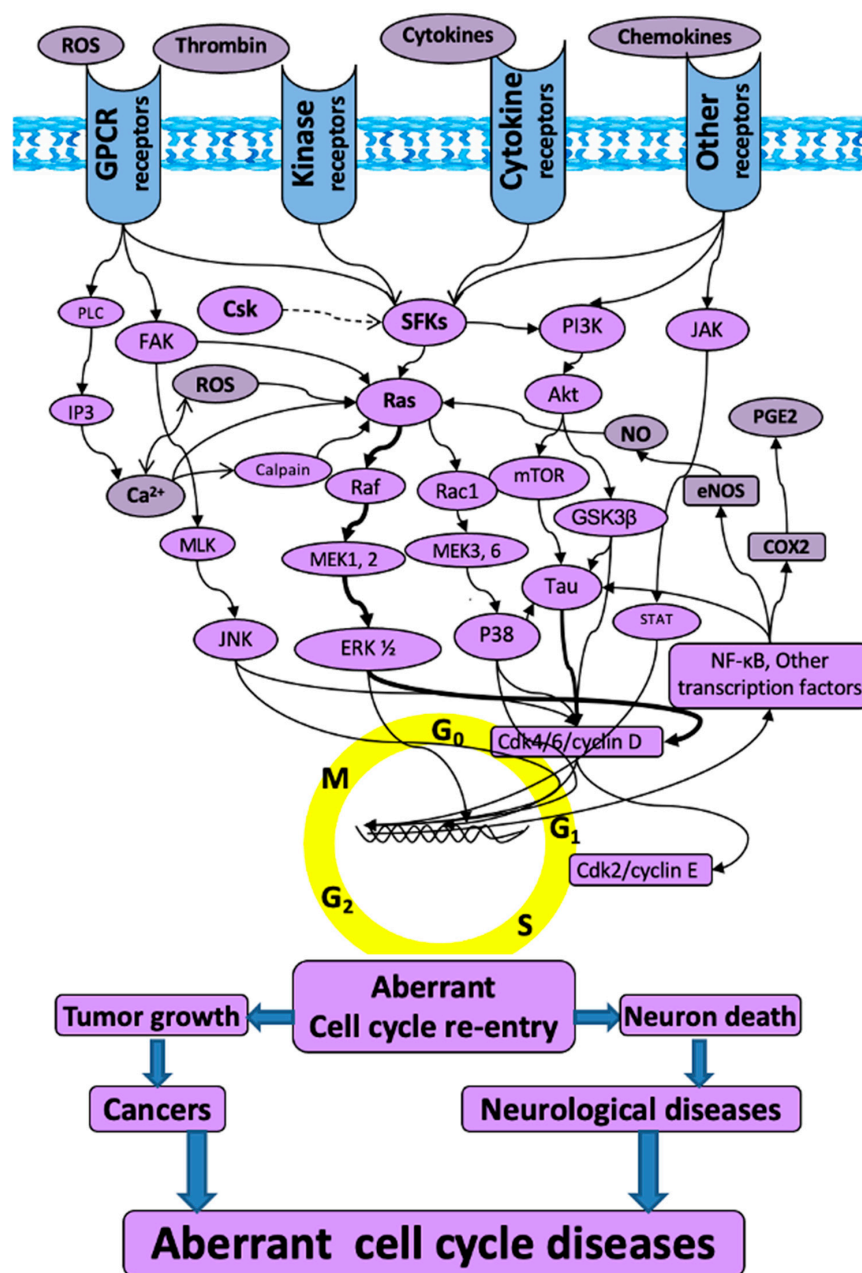
**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

We developed a novel concept of “Aberrant Cell Cycle Disease” (ACCD), revealing that two major types of diseases, cancers and neurological diseases, share the same mechanism of “aberrant cell cycle re-entry” that is manifested as oncogene/kinase activation and/or tumor suppressor inhibition [1]. This concept is an innovation by combining two series of discoveries: (1) tumor cell growth due to aberrant cell cycle re-entry in cancers [2–4]; and (2) neuronal death due to aberrant cell cycle re-entry in neurological disorders [5–18]. The ACCD concept itself is novel in two aspects: (1) revealing that cancers and neurological disorders (including TBI) share a common mechanism of aberrant cell cycle re-entry, manifested as kinase/oncoprotein activation and tumor suppressor inactivation [1]; and (2) expanding the key “cell cycle players” from cyclin-dependent kinases (CDKs) and cyclins to Src family kinase (SFK), Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and other numerous kinases (Figure 1) [1].

Since kinases are implicated in the process of the cell cycle, kinase inhibitors should be able to block the cell cycle for the treatment of both cancers and neurological disorders. Indeed, compelling evidence shows that a single agent inhibiting the same kinase(s) can treat both cancers and neurological disorders. There is a long list of such agents: CDK inhibitor (roscovitine), SFK inhibitor (PP2), ERK inhibitor (PD98059), ROCK inhibitor (Y-27632), STAT inhibitor (WP1066), mTOR inhibitor (RAD001), and Wnt inhibitor (CWP232291), amongst others. For example, several labs reported that the Src inhibitor PP2 kills cancer

cells [19–21], while we showed that PP2 protects neurons following acute brain injury in rats [22–24].



**Figure 1.** The schematic of “aberrant cell cycle diseases”. The molecules and related mitogenic pathways contributing to the aberrant cell cycle re-entry that is associated with not only tumorigenesis in cancers, but also neuronal death in neurological diseases. The arrows do not necessarily indicate direct binding and/or activation of the downstream molecules; intermediate proteins or kinases may exist. Akt: protein kinase B; Ca<sup>2+</sup>: calcium; Cdk: cyclin-dependent kinase; COX2: cyclooxygenase-2; Csk: c-terminal Src kinase; eNOS: endothelial nitric oxide synthase; ERK: extracellular signal-regulated kinase; FAK: focal adhesion kinase; GPCR: G protein-coupled receptor; GSK3β: glycogen synthase-3 beta; IP3: inositol trisphosphate; JAK: Janus kinase; JNK: c-Jun N-terminal kinases; MEK: mitogen-activated protein kinase kinase; MLK: mixed lineage kinases; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa B; NO: nitric oxide; PGE2: prostaglandin E2; PI3K: phosphatidylinositol 3-kinase; PLC: phospholipase C; Ras: rat sarcoma virus kinase; Rac1: ras-related C3 botulinum toxin substrate 1; Raf: rapidly accelerated fibrosarcoma; ROS: reactive oxygen species; SFKs: Src family kinases; STAT: signal transducer and activator of transcription.

Following the golden era of cancer drug development in the past few decades, the United States Food and Drug Administration (US FDA) has approved numerous cancer therapies (e.g., RNAi gene therapy, nanoparticle-based in vivo drug delivery reagents, kinase-targeted drugs, and CAR T-cell therapy, as well as others). In contrast, there are very few FDA-approved drugs that benefit patients with certain neurological disorders, such as Alzheimer's disease (AD), intracerebral hemorrhage (ICH), ischemic stroke (IS), traumatic brain injury (TBI), and other disorders. If state-of-the-art approaches of cancer therapies can be applied to neurological treatments, new breakthroughs will very likely arise in the development of neurological drugs.

The "Aberrant Cell Cycle Disease" concept links cancers and neurological diseases due to their common mechanisms, providing the theoretical framework to leverage cancer elements (e.g., oncogene inhibition) for the treatment of neurological diseases. Since the approval of the first kinase inhibitor (imatinib) in 2001, the US FDA approved a total of 74 kinase inhibitors by the end of 2021, with 12 of these (i.e., tepotinib, umbralisib, idelalisib, duvelisib, copanlisib, alpelisib, tivozanib, trilaciclib, infigratinib, belumosudil, mobocertinib, and asciminib) being approved in 2021.

In this review, we summarize the FDA-approved kinase inhibitors and highlight those that have been tested in experimental models and/or clinical trials for the treatment of neurological disorders, with a purpose of discussing the feasibility and applicability of repurposing these cancer drugs (FDA-approved kinase inhibitors) for the treatment of neurological disorders (e.g., AD, ICH, IS, TBI, and others). Numerous tumor suppressors and non-FDA approved kinase inhibitors are beyond the scope of this review.

## 2. Kinases, Oncoproteins, and Tumor Suppressors

Kinases exist universally in various species, ranging from bacteria to mold to worms and mammals. The human genome encodes more than 500 protein kinases that catalyze various reactions of phosphorylation where high-energy molecules (e.g., ATP) donate phosphate groups to substrate molecules [25,26]. Phosphorylation and its reverse (e.g., dephosphorylation that is catalyzed by phosphatases) are the most frequent post-translational modifications to regulate protein activity. Approximately 13,000 human proteins have phosphorylation sites [27]. Pertaining to their target substrates, human protein kinases are classified as serine–threonine kinases (STK), tyrosine kinases (TK), and dual specificity kinases (STK/TK). Based on the presence or absence of transmembrane receptor structures, TKs can be further divided into receptor TK (RTK) and non-receptor TK (NRTK).

Kinases have predominantly been thought of as oncogenes involved in tumorigenesis [28], since genome-wide studies of kinases have revealed that genetically inherited variants of specific kinases mediate cancer initiation, promotion, and progression, as well as recurrence [29], when they are constitutively overexpressed and/or continuously activated due to chromosomal reshuffling and genetic mutations [29]. However, increasing evidence has shed light on an opposite role for kinases as tumor suppressors. The first identified tumor-suppressing kinase was the protein kinase C (PKC) family members that generally function as tumor suppressors [30]. Subsequently, MKK4 of the mitogen-activated protein kinase kinase (MAPKK) family and DAPK3 of the death-associated protein kinase (DAPK) family were revealed as tumor suppressors, although some controversy still remains [28].

## 3. Neurological Disorder Subtypes and FDA-Approved Drugs for Neurological Treatment

Neurological disorders are diseases of the central and peripheral nervous system. There are more than 600 different neurological disorders, including several main subtypes: (1) acute brain injury, such as ischemic stroke (IS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), spinal cord injury (SCI), epilepsy, and others; (2) neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and others; (3) neurodevelopment diseases, such as autism spectrum disorder (ASD) and cerebral palsy, as well as

others; (4) infectious diseases, such as meningitis and encephalitis; and (5) neurological tumors, such as neuroblastoma (NB), glioblastoma (GBM), glioma, and others. Moreover, neurological disorders are often accompanied by mental syndromes, such as when TBI survivors (e.g., 10%–20% of the civilian population and up to 50% of military populations) are subsequently diagnosed with post-traumatic stress disorder (PTSD) [31–33], and stroke patients often suffer depression and/or anxiety [34].

These neurological disorders affect hundreds of millions worldwide per year. For example, AD is the most common cause of dementia and represents 60–70% of a total of 47.5 million dementia cases worldwide with 7.7 million new cases every year. The all-cause and all-severity TBIs are estimated to affect ~69 million people each year [35]. More than 6 million people die because of strokes (e.g., IS, ICH) worldwide each year. However, the US FDA has so far approved only one drug (tissue plasminogen activator—tPA) for the treatment of IS and one monoclonal antibody drug (aducanumab) for the treatment of AD, but no drugs have been approved for the treatment of TBI and ICH. In regard to these two FDA-approved neurological drugs, tPA only benefits a small proportion of IS patients, while aducanumab is controversial, as it was approved on the basis that it is capable of reducing a surrogate biomarker, amyloid in the brain, but not on any evidence of clinical benefit. Overall, there are dire unmet needs of effective FDA-approved drugs for the treatment of stroke, TBI, AD, and other neurological disorders.

#### 4. FDA-Approved Kinase Inhibitors

Since the approval of the first kinase inhibitor (imatinib) in 2001, the US FDA has so far approved a total of 74 kinase inhibitors, with 12 kinase inhibitors approved in a single year of 2021. Most approved kinase drugs are active against cancers, with a few exceptions for the treatment of non-oncological indications (e.g., tofacitinib for rheumatoid arthritis, sirolimus for organ rejection, nintedanib for idiopathic pulmonary fibrosis). It appears that an increasing number of kinase inhibitors will be approved in the near future, since more than 130 kinase inhibitors were reported to be in Phase-2/3 of clinical trials in 2015 [26]. It is beyond the scope of this review to discuss other protein kinase inhibitors than those approved by FDA.

There are numerous kinase drugs approved for one single indication (Table S1). For example, imatinib, nilotinib, dasatinib, bosutinib, and ponatinib have all been approved for chronic myeloid leukemia (CML). Vandetanib, cabozantinib, and levantinib are used for the treatment for medullary thyroid carcinoma, while imatinib, sunitinib, and regorafenib are indicated also for gastrointestinal stromal tumor (GIST).

Some approved kinase inhibitors have been tested for the treatment of cancer types other than their original indication. For example, abemaciclib, originally approved for the treatment of advanced or metastatic breast cancer in 2015, was recently approved for combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with early breast cancer at high risk of recurrence [36]. In addition, some kinase inhibitors have been used in conjunction for certain cancer treatments (e.g., vemurafenib or dabrafenib in combination with trametinib for the treatment of metastatic melanoma) [37].

##### 4.1. FDA-Approved Kinase Inhibitors in Clinical Trials for Neurological Disorders

Many of the FDA-approved kinase inhibitors have been tested in clinical and pre-clinical trials for neurological disorders, though none of them have been approved by the FDA for neurological treatment (Table S1). In terms of clinical trials, Baricitinib, a JAK inhibitor, is being studied in a phase II trial (NCT03921554) along with a phase II and III trial (NCT04517253), for efficacy and safety in Aicardi–Goutieres Syndrome, an inherited encephalopathy that affects infants and usually results in severe mental and physical disabilities.

Bosutinib, an inhibitor of Src and Bcr-Abl, is and has been investigated in clinical trials for different neurodegenerative disorders. There is a phase I trial (NCT04744532)



studying the safety and tolerability of bosutinib for amyotrophic lateral sclerosis (ALS), a progressive neurological disease leading to loss of muscle control. The safety, tolerability, and clinical outcomes of bosutinib on patients with dementia with Lewy bodies has also been studied in a completed phase 2 trial (NCT03888222). In preclinical studies, it has been found that bosutinib reduces levels of alpha-synuclein, tau, and beta-amyloid in the CNS, and improves motor and cognitive behavior in animal models [38–40]. Bosutinib was also found to promote autophagy and clear protein aggregates in neurons [41,42]. There is also an ongoing phase I trial (NCT02921477) studying the safety and tolerability of bosutinib for mild cognitive impairment (MCI) and dementia.

Cobimetinib, an MEK inhibitor, has been studied in a phase 2 trial (NCT04079179) studying its safety and efficacy in histiocytic disorders, which can lead to neurodegeneration. Dasatinib, an inhibitor of Src, Bcr-Abl, Kit, EGFR, PDGFR, and EPH (EphA2), has been studied in multiple clinical trials examining its effectiveness in treating AD and mild cognitive impairment. Particularly, in four clinical trials (NCT04063124—phase I and II, NCT04785300—phase I and II, NCT04685590- phase II, NCT05422885—phase I/II), the safety, feasibility, and efficacy of dasatinib and quercetin, a flavonoid known to have antioxidant and anti-inflammatory effects, are being assessed.

Everolimus, an inhibitor of mTOR and FKBP, has been extensively evaluated in clinical trials studying different acute brain injury disorders, neurodegenerative disorders, and neurodevelopmental disorders. A phase II trial (NCT03198949) studying the safety and anti-epileptic efficacy of everolimus in patients with Epilepsy and focal cortical dysplasia II, who have failed more than two antiepileptic drugs and surgery, has been recently completed. Everolimus has been shown in animal models to protect seizure-induced brain injury and reduce neuroinflammation associated with seizures [43,44]. A phase II trial (NCT00857259) evaluating the safety and efficacy of everolimus with or without ranibizumab in patients with neovascular age-related macular degeneration, a neurodegenerative disorder that results in a loss of central vision, is currently in progress. Additionally, in a phase I and II trial (NCT02991807), researchers studied whether everolimus can improve neurocognitive outcomes in patients with hamartoma tumor syndrome caused by a PTEN germline mutation. There are also multiple studies (NCT02962414, NCT01730209, NCT01070316, NCT01713946, NCT02451696, NCT01954693, NCT01929642, and NCT012899-12) evaluating the safety and efficacy of everolimus in patients with tuberous sclerosis complex, which is often associated with refractory seizures, cognitive disabilities, autism, focal cortical dysplasia, other neurocognitive problems, and self-injury. Lastly, there is a phase II trial that studied the safety and efficacy of everolimus in patients with seizures who have Sturge–Weber syndrome, a rare disease in which tumors form in the brain (NCT01997255).

Imatinib, a Bcr-Abl, Kit and PDGFR inhibitor, has been studied in several acute brain injury and neurodegenerative disorders. In a phase III trial (NCT03639922), imatinib was studied in ischemic stroke patients to determine whether there was improvement in functional outcomes. Imatinib, administered for 6 days, was added to conventional stroke therapy and started within 8 days of the onset of stroke. Additionally, in a phase II trial (NCT02363361), the safety, uptake, and tolerability of imatinib is being studied in patients with cervical SCI. A phase II trial (NCT03674099) is currently testing imatinib as a novel therapy for multiple sclerosis, comparing its efficacy to methylprednisolone, the standard of care drug for multiple sclerosis relapses. Lastly, imatinib had been studied in a phase I trial (NCT00403156), examining choroidal neovascularization, although this study has been withdrawn.

Nilotinib is a kinase inhibitor that inhibits the activity of Bcr-Abl, PDGFR and DDR1. It has been studied in several neurodegenerative diseases in clinical trials. In a phase I study, nilotinib (NCT03764215) was administered to patients with Huntington disease. Biomarkers, such as phosphorylated tau levels, and functional outcomes were assessed. In an ongoing phase II study (NCT04002674), the use of nilotinib in patients with dementia with Lewy bodies is being studied, particularly on the pharmacokinetics, tolerability, biomarkers, and safety of use. In a phase II study (NCT02947893), the efficacy of nilotinib

in AD was studied. Specifically, the effects of nilotinib on cell death was detected with cell markers, and the amyloid concentrations in the brain were assessed with PET scans. Also, a recent phase III clinical trial (NCT05143528) is currently studying the safety and efficacy of nilotinib in patients with early AD using two different dosages. There are also three studies that examined the effects of nilotinib in patients with Parkinson's disease (NCT02954978, NCT02281474, NCT03205488). In a phase II trial (NCT03932669), the efficacy and adverse events of nilotinib are being studied in patients with spinocerebellar ataxia. In particular, improvement in daily living performance and cerebellar functions are being assessed.

Pazopanib inhibits the activities of VEGFR 1/2/3, PDGFR  $\alpha/\beta$ , FGFR 1/3, Kit, Lck, Fms, and Itk. In terms of neurological disease settings, it is studied mainly in macular degeneration (NCT00659555, NCT01154062, NCT00612456, NCT01072214, NCT00463320, NCT01362348, NCT01134055, NCT01051700, and NCT00733304). Regorafenib, a VEGF kinase inhibitor, was studied in neovascular age-related macular degeneration. After successfully passing phase I clinical trials, (NCT02222207), phase IIa trials were terminated after the results were less effective than the current gold standard treatment [45].

Sirolimus, an mTOR inhibitor initially used as an immunosuppressant in kidney transplants, has been repurposed in a multitude of neurological and psychiatric clinical trials, including cerebral aneurysms (NCT04141020), epilepsy (NCT03646240), Alzheimer's disease (NCT04629495 and NCT04200911), frontotemporal dementia (NCT04408625), amyotrophic lateral sclerosis (NCT03359538), Parkinson's disease (NCT04127578), age-related macular degeneration (NCT01445548, NCT00766649, NCT00712491, NCT02357342, NCT02732899, NCT00766337, and NCT00304954), multiple sclerosis (NCT00095329), geographic atrophy associated with age-related macular degeneration (NCT01675947), multiple system atrophy (NCT03589976), Sturge-Weber syndrome (NCT03047980 and NCT02080624), lysosomal diseases (NCT03952637), Leigh syndrome (NCT03747328), tuberous sclerosis complex (NCT04595513, NCT01929642, and NCT05104983), Gaucher disease type 2 (NCT04411654), diabetic retinopathy (NCT00711490), diabetic macular edema (NCT00656643 and NCT00401115), alcohol use disorder (NCT03732248), smoking cessation (NCT04161144), depression (NCT02487485), and stroke prevention (NCT04948749).

Of the 32 clinical trials, two have completed phase I (NCT00401115 and NCT03732248), one has completed phase II/III (NCT03047980), 11 have completed phase I/II or II trials (NCT01445548, NCT00766649, NCT02357342, NCT02732899, NCT00304954, NCT02080624, NCT01929642, NCT00711490, NCT00656643, NCT04161144, and NCT02487485), six have been withdrawn or terminated in phases I/II (NCT00095329, NCT00712491, NCT01675947, NCT03589976, NCT00766337, and NCT03747328), nine are currently in phase I/II or II (NCT04141020, NCT04629495, NCT03359538, NCT04408625, NCT04127578, NCT03952637, NCT04595513, NCT04411654, and NCT05104983), two are in phase I (NCT03646240 and NCT04200911), and one does not specify the phase of the trial (NCT04948749).

Sunitinib is a tyrosine kinase inhibitor, which has been studied in clinical trials to treat both neovascular age-related macular degeneration and diabetic macular edema secondary to retinal vein occlusion. The clinical use of sunitinib for neovascular age-related macular degeneration (NCT03249740) completed phase I clinical trials in 2019. This study tested increasing doses of sunitinib injected intravitreally compared to aflibercept. No data has been published at this time. The use of sunitinib for diabetic macular edema secondary to retinal vein occlusion (NCT04085341) completed phase II trials in 2021. This study specifically looked at the dosing of this compound in patients who had prior treatment with anti-vascular endothelial growth factor.

Temsirolimus, a prodrug of sirolimus and an mTOR inhibitor, has been used in clinical trials for relapsing–remitting multiple sclerosis (NCT00228397). Phase II clinical trials were conducted to assess the long-term tolerability and safety of three different doses of temsirolimus. Tofacitinib, a janus kinase enzyme inhibitor, has been used in three different clinical trials involving neurological disorders: myasthenia gravis, Down syndrome, and depression. Recruiting is underway for an early phase I trial to use tofacitinib in patients with myasthenia gravis (NCT04431895) with the goal to significantly improve quantita-

tive myasthenia gravis scores from a baseline measurement after six months. Currently, a phase II trial using tofacitinib in patients with Down syndrome to treat a multitude of different skin conditions (alopecia areata, atopic dermatitis/eczema, psoriasis, etc.) (NCT04246372) is underway. Lastly, a phase I/II clinical trial comparing tofacitinib to placebo to treat treatment-resistant depression (NCT04141904) had been suspended due to the COVID-19 pandemic.

Trametinib, an MEK inhibitor, is being used in a phase I/II clinical trial for amyotrophic lateral sclerosis (NCT04326283). In this study, researchers will focus on the safety, tolerability, and efficacy of trametinib in ALS patients. Upadacitinib, a selective JAK1 inhibitor, is currently going through phase III trials to treat giant cell arthritis (NCT03725202). In this study, the efficacy of upadacitinib plus corticosteroids is being assessed compared to corticosteroids alone. Finally, a recent phase II trial (NCT05356858) is studying the efficacy and safety of zanubrutinib, a BTK inhibitor, in patients with recurrent neuromyelitis optica spectrum disease, a disease where the immune system damages the optic nerves and spinal cord.

#### 4.2. FDA-Approved Kinase Inhibitors in Preclinical Trials for Neurological Disorders

While there have been 16 FDA-approved kinase inhibitors in clinical trials for neurological disorders, there are numerous preclinical studies of FDA-approved kinase inhibitors evaluating their effects on neurological disorders. Abemaciclib has been studied in preclinical models for the treatment of motor neuron degeneration [46] and post-traumatic stress disorder [47]. Afatinib has been tested in preclinical models for the treatment of oxygen/glucose deprivation-induced neuroinflammation [48], multiple sclerosis [49], autoimmune CNS inflammation [49], and nicotine dependence [50]. Axitinib has been tested for treatment of AD [51]. Alectinib has been tested for the potential treatment of binge drinking [52,53]. Baricitinib has been tested in preclinical models for the potential treatment of neurocognitive disorders induced by HIV [54], encephalitis [55,56], multiple sclerosis [56], hypersensitivity in Down syndrome [57], acute spinal cord injury [58], Hutchinson–Gilford progeria [59], and AD [60]. Binimetinib has been shown in a preclinical study to be a potential treatment for some forms of AD [61]. Bosutinib has been tested for the potential treatment of intracerebral hemorrhage [62], cerebral ischemia [63],  $\alpha$ -synucleinopathies and tauopathies in neurodegeneration [40,41], Parkinson’s disease [38,42,64], TDP-43 pathology [65], SIN1-mediated neurotoxicity [66], and botulinum neurotoxins [67]. Cabozantinib has been tested for the potential treatment of Rett syndrome [68] and AD [69].

Crizotinib has been tested for the potential treatment of Parkinson’s disease [70], AD [71], persistent pain [72], *Toxoplasma gondii* (can result in symptoms of congenital neurological and meningoencephalitis) [73], and craniosynostosis associated with Saethre–Chotzen syndrome [74]. Dabrafenib has been tested for the potential treatment of ischemic brain injury [75], spinal cord injury [76], Parkinson’s diseases [77,78], and ataxia caused by neurohistiocytosis of the cerebellum [79]. Dasatinib has been tested for the potential treatment of traumatic brain injury [80], lipopolysaccharide-induced neuroinflammation [81], kainic acid-induced neuroinflammation [82], glaucoma [83], tau-associated pathology [84], multiple sclerosis [85], amyotrophic lateral sclerosis [86–88], Parkinson’s disease [87], age-related blood brain barrier dysfunction [89], age-related cognitive dysfunction [89,90], obesity-induced anxiety [91], chronic unpredictable stress-induced cognitive deficits [92], fetal alcohol syndrome [93], and botulinum neurotoxins [67]. Erlotinib has been tested for the potential treatment of nerve fiber injury [94], intracranial aneurysm formation [95], amyotrophic lateral sclerosis [96], diabetic peripheral neuropathy [97,98], and amyloid- $\beta$ -induced memory loss [99].

Everolimus has been tested for the potential treatment of encephalopathy of prematurity [100], atherosclerosis-associated brain hypoxia [101], ischemic stroke [102–104], Alzheimer’s disease [105,106], Huntington disease [107,108], vascular dementia [109], lipopolysaccharide-induced neuroinflammation [110], insulin dysfunction-related cognitive dysfunction [111], glutamate-induced neurotoxicity [112], Guillain–Barre syndrome [113], mul-



multiple sclerosis [114], tuberous sclerosis complex-associated autism-like social deficits [115,116], and Lafora disease [117]. Fedratinib has been tested for the potential treatment of ischemic stroke [118], intracerebral hemorrhage [119], Wernicke's encephalopathy [120,121], and Alzheimer's disease [122]. Gefitinib has been tested for the potential treatment of spinal cord injury [123], amyloid- $\beta$ -induced memory loss [99], schizophrenia [124], *Streptococcus pneumoniae* meningitis [125], and *Toxoplasma gondii* (can result in symptoms of congenital neurological and meningoencephalitis) [73,126].

Ibrutinib has been tested for the potential treatment of ischemic stroke [127,128], spinal cord injury [129,130], age-related cognitive deterioration [131], Alzheimer's disease [132,133], lipopolysaccharide-induced neuroinflammation [134], anxiogenic behavior [135], depression [136,137], and cocaine use disorder [138]. Imatinib has been tested for the potential treatment of subarachnoid hemorrhage [139–144], intracerebral hemorrhage [145–148], cerebral small vessel disease [149], traumatic brain injury-induced seizures [150], seizures [150,151], traumatic brain injury [152], ischemia reperfusion-induced cerebral injury [153,154], Alzheimer's disease [155–170], Parkinson's disease [171–174], prion diseases [175–178], amyotrophic lateral sclerosis [179], Huntington's diseases [180], cerebral malaria [181], hypoxic ventilatory depression [182], Niemann–Pick type C disease [183], Niemann–Pick type A disease [184], Gaucher disease [185], simian human immunodeficiency virus encephalitis [186], and morphine tolerance [187]. Lapatinib has been tested for the potential treatment of epileptic seizures [188], organophosphate-induced axonal damage in spinal cord [189], and Alzheimer's disease [190,191]. Lorlatinib has been tested for the potential treatment of persistent pain [72]. Midostaurin has been tested for the potential treatment of traumatic spinal cord injury [192]. Neratinib has been tested for the potential treatment of AD [193].

Nilotinib has been tested for the potential treatment of epileptic seizures [194], tauopathies [40,41,195], alpha-synucleinopathies [40,42,196–198], TDP-43 pathology [64,65], beta-amyloid pathology [195], AD [60,199–201], Parkinson's disease [202–204], chorea-acanthocytosis [205,206], and Niemann–Pick type A disease [184]. Palbociclib has been tested for the potential treatment of spinal muscular atrophy [207], amyloid beta-peptide pathology [208], and Parkinson's disease [209]. Pazopanib has been tested for the potential treatment of tauopathy [210] and neurodegeneration-induced memory and cognitive deficits [211]. Pexidartinib has been tested for the potential treatment of intracerebral hemorrhage [212,213], subarachnoid hemorrhage [214], obesity-related cerebrovascular dysfunction [215], cognitive decline due to brain damage [216], tauopathy [217], AD [218,219], Huntington's disease [220], multiple sclerosis [221–223], spinocerebellar ataxia type 1 [224], Down syndrome [225], peripheral nerve injury-induced mechanical hypersensitivity [226], cocaine addiction [227], and Parkinson's disease [228]. Ponatinib has been tested for the potential treatment of ischemic stroke [229], epilepsy [230], and cerebral cavernous malformation [231].

Regorafenib has been tested for the potential treatment of AD [232]. Ruxolitinib has been tested for the potential treatment of Parkinson's disease [233], multiple sclerosis [234,235], Down syndrome [236], cytokine-induced blood brain barrier dysfunction [237], HIV-associated neurocognitive disorders [238], depression-like behaviors and cognitive defects [239], traumatic brain injury [240], ischemic stroke [241], and spinal cord injury [242]. Selumetinib has been tested for the potential treatment of frontotemporal lobar degeneration [243], obsessive-compulsive disorder [244], acrolein-induced neurotoxicity [245], and intracerebral hemorrhage [246].

Sirolimus has been tested for the potential treatment of ischemic stroke [102,247–278], traumatic brain injury [279–286], subarachnoid hemorrhage [287–293], spinal cord injury [294–303], germinal matrix hemorrhage [304,305], intracerebral hemorrhage [306–308], seizure-induced memory deficits [309–312], seizure in Leigh syndrome [313], spinal cord ischemia [314,315], preganglionic cervical root transection [316], optic nerve crush [317], alveolar nerve transection [318], ischemic retinal disease [319], multiple sclerosis [320–331], Parkinson's disease [332–335], cerebral palsy [336], prion disease [337–339], AD [340–344], vascular dementia [345], diabetes-induced AD-like pathology [346], diabetes-induced neu-

rotopathology [347], Huntington disease [348–353], macular degeneration [354], degenerative optic nerve disease [355], retinal neurodegeneration [356], cadmium-induced neurodegeneration [357–360], spiral ganglion neurons degeneration [361], tauopathy [362,363], synucleinopathy [364–366], myasthenia gravis [367,368], iron-induced cognitive impairments [369], intermittent hypoxia-induced cognitive impairments [370], cannabinoid-induced cognitive impairments [371], diabetic perioperative neurocognitive disorders [372], ethanol-induced neurodegeneration [373], aging-related neurodegeneration [374], methylmercury-induced neurotoxicity [375], TDP-43 proteinopathy [376], amyotrophic lateral sclerosis [377], autism spectrum disorders [378–384], autism-associated behavioral disorders [385], Krabbe disease [386], Down syndrome [387–390], intellectual disability [391], fetal alcohol spectrum disorders [392–394], autism associated with tuberous sclerosis [395–398], tuberous sclerosis complex [399–401], neurodevelopmental defects in tuberous sclerosis complex [402,403], cognitive deficits in tuberous sclerosis complex [404,405], polyhydramnios, megalencephaly, and symptomatic epilepsy syndrome [406], focal cortical dysplasia [407], epilepsy [408,409], epilepsy-induced anxiety and depression [410], Schaaf-Yang syndrome [411], cerebral malaria [412–414], neuropathic pain [415], seizure-induced anxiety [416], obesity-induced anxiety and depression [417], mitochondrial encephalopathy [418], diabetes mellitus-related cognitive deficits [419–421], nicotine addiction [422], alcohol-related disorders [402,423,424], herpes simplex virus encephalitis [425], depression [426], mania [427], porcine hemagglutinating encephalomyelitis virus [428], anxiety disorders [429–431], photochemical damage in retinal photoreceptor cells [432], multisystem proteinopathy [433], NMDA-induced retinal damage [434–436], adverse optineurin phenotypes [437], hydrocephalus [438], sleep disorders [439], sepsis-induced cognitive impairment [440], drug-seeking behavior [441–443], aging-induced neuroinflammation [444], Koolen–de Vries syndrome [445], TANC2 mutation-induced neuropsychiatric disorders [446], general anesthetic-induced neurodevelopmental disease in fragile-X syndrome [447], *Helicobacter pylori*-induced depressive and anxiety behavior [448], and age-related hearing loss [449].

Sorafenib has been tested for the potential treatment for subarachnoid hemorrhage [450], ischemic stroke [451], spinal cord injury [452], AD [69,453,454], Parkinson’s disease [455], multiple sclerosis [456,457], rabies [458], Rift Valley fever virus [459], alphaviruses [460], and Picornavirus enterovirus 71 [461]. Sunitinib has been tested for the potential treatment for traumatic brain injury [462], seizure [463], AD [464–466], Rett syndrome [68], cognitive impairment associated with HIV [467,468], dengue virus [469], and rabies [470]. Temsirolimus has been tested for the potential treatment for spinal cord injury [300], Parkinson’s disease [471,472], tauopathy [473,474], AD [475], spinocerebellar ataxia type 3 [476], nicotine withdrawal-associated cognitive deficits [477], and X-linked adrenoleukodystrophy [478]. Tofacitinib has been tested for the potential treatment for ischemic stroke [479], AD [480], multiple sclerosis [481,482], Parkinson’s disease [483], amyotrophic lateral sclerosis [484], and Venezuelan equine encephalitis virus [485]. Trametinib has been tested for the potential treatment for traumatic brain injury [486], aneurysmal subarachnoid hemorrhage [487], and brain arteriovenous malformations [488]. Vandetanib has been tested for the potential treatment for germinal matrix hemorrhage [489]. Lastly, Infigratinib has also been tested as a potential treatment for diabetic retinopathy [490].

## 5. Conclusions and Discussions

In summary, there are 16 FDA-approved kinase inhibitors that have been tested in clinical trials for neurological treatments. Since almost all 74 FDA-approved kinase inhibitors have been examined in various animal models of neurological disorders, it appears that more FDA-approved kinase inhibitors will enter clinical trials for neurological treatments in the future. In accordance with the Generics and Biosimilars Initiative, the FDA-approved drugs (including kinase inhibitors) will become available commercially at relatively low prices after expiration of their existing patents. We are optimistic that this repurposing strategy is likely to provide safe, effective, and affordable therapies for neurological disorders.

It is important to note that kinases are also involved in the division of neural stem cells that are associated with neurogenesis and self-repair after brain injury. Therefore, optimization of the dosing regimen of a kinase inhibitor or the combination of a few kinase inhibitors is needed to increase efficacy while reducing side effects, when repurposing the kinase inhibitor(s) to treat neurological disorders.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ph15121546/s1>, Table S1: FDA-approved kinase inhibitors in preclinical and clinical trials for neurological disorders.

**Author Contributions:** A.L., J.V., D.P., D.L., D.X., O.A., T.E., T.D. and M.G. reviewed the literature and wrote the manuscript. A.L. created the table, R.M. edited the manuscript, and D.-Z.L. developed the concept. All authors have read and agreed to the published version of the manuscript.

**Funding:** We acknowledge the support of NIH/NINDS grants (R01NS089901 and R01NS114061 to D.-Z.L.).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data sharing not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Disclosure:** Figure 1 was modified from the figure published previously in *Neural Regen Res.* **2017**, *12*, 910–911.

## References

- Liu, D.Z.; Ander, B.P. Cell cycle inhibition without disruption of neurogenesis is a strategy for treatment of aberrant cell cycle diseases: An update. *Sci. World J.* **2012**, *2012*, 491737. [[CrossRef](#)] [[PubMed](#)]
- Hartwell, L.H. Nobel Lecture. Yeast and cancer. *Biosci. Rep.* **2002**, *22*, 373–394. [[CrossRef](#)] [[PubMed](#)]
- Hunt, T. Nobel Lecture. Protein synthesis, proteolysis, and cell cycle transitions. *Biosci. Rep.* **2002**, *22*, 465–486. [[CrossRef](#)]
- Nurse, P.M. Nobel Lecture. Cyclin dependent kinases and cell cycle control. *Biosci. Rep.* **2002**, *22*, 487–499. [[CrossRef](#)]
- Busser, J.; Geldmacher, D.S.; Herrup, K. Ectopic cell cycle proteins predict the sites of neuronal cell death in Alzheimer's disease brain. *J. Neurosci.* **1998**, *18*, 2801–2807. [[CrossRef](#)]
- Herrup, K.; Yang, Y. Cell cycle regulation in the postmitotic neuron: Oxymoron or new biology? *Nat. Rev. Neurosci.* **2007**, *8*, 368–378. [[CrossRef](#)] [[PubMed](#)]
- Ding, X.L.; Husseman, J.; Tomashevski, A.; Nochlin, D.; Jin, L.W.; Vincent, I. The cell cycle Cdc25A tyrosine phosphatase is activated in degenerating postmitotic neurons in Alzheimer's disease. *Am. J. Pathol.* **2000**, *157*, 1983–1990. [[CrossRef](#)]
- Osuga, H.; Osuga, S.; Wang, F.; Fetni, R.; Hogan, M.J.; Slack, R.S.; Hakim, A.M.; Ikeda, J.E.; Park, D.S. Cyclin-dependent kinases as a therapeutic target for stroke. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 10254–10259. [[CrossRef](#)]
- Vincent, I.; Bu, B.; Hudson, K.; Husseman, J.; Nochlin, D.; Jin, L. Constitutive Cdc25B tyrosine phosphatase activity in adult brain neurons with M phase-type alterations in Alzheimer's disease. *Neuroscience* **2001**, *105*, 639–650. [[CrossRef](#)]
- Di Giovanni, S.; Knobloch, S.M.; Brandoli, C.; Aden, S.A.; Hoffman, E.P.; Faden, A.I. Gene profiling in spinal cord injury shows role of cell cycle in neuronal death. *Ann. Neurol.* **2003**, *53*, 454–468. [[CrossRef](#)]
- Di Giovanni, S.; Movsesyan, V.; Ahmed, F.; Cernak, I.; Schinelli, S.; Stoica, B.; Faden, A.I. Cell cycle inhibition provides neuroprotection and reduces glial proliferation and scar formation after traumatic brain injury. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 8333–8338. [[CrossRef](#)] [[PubMed](#)]
- Hilton, G.D.; Stoica, B.A.; Byrnes, K.R.; Faden, A.I. Roscovitine reduces neuronal loss, glial activation, and neurologic deficits after brain trauma. *J. Cereb. Blood Flow Metab.* **2008**, *28*, 1845–1859. [[CrossRef](#)] [[PubMed](#)]
- Kabadi, S.V.; Stoica, B.A.; Byrnes, K.R.; Hanscom, M.; Loane, D.J.; Faden, A.I. Selective CDK inhibitor limits neuroinflammation and progressive neurodegeneration after brain trauma. *J. Cereb. Blood Flow Metab.* **2012**, *32*, 137–149. [[CrossRef](#)]
- Skovira, J.W.; Wu, J.; Matyas, J.J.; Kumar, A.; Hanscom, M.; Kabadi, S.V.; Fang, R.; Faden, A.I. Cell cycle inhibition reduces inflammatory responses, neuronal loss, and cognitive deficits induced by hypobaric exposure following traumatic brain injury. *J. Neuroinflamm.* **2016**, *13*, 299. [[CrossRef](#)] [[PubMed](#)]
- Aubrecht, T.G.; Faden, A.I.; Sabirzhanov, B.; Glaser, E.P.; Roelofs, B.A.; Polster, B.M.; Makarevich, O.; Stoica, B.A. Comparing effects of CDK inhibition and E2F1/2 ablation on neuronal cell death pathways in vitro and after traumatic brain injury. *Cell Death Dis.* **2018**, *9*, 1121. [[CrossRef](#)] [[PubMed](#)]

16. Joseph, C.; Mangani, A.S.; Gupta, V.; Chitranshi, N.; Shen, T.; Dheer, Y.; Kb, D.; Mirzaei, M.; You, Y.; Graham, S.L.; et al. Cell Cycle Deficits in Neurodegenerative Disorders: Uncovering Molecular Mechanisms to Drive Innovative Therapeutic Development. *Aging Dis.* **2020**, *11*, 946–966. [[CrossRef](#)] [[PubMed](#)]
17. Barrio-Alonso, E.; Hernandez-Vivanco, A.; Walton, C.C.; Perea, G.; Frade, J.M. Cell cycle reentry triggers hyperploidy and synaptic dysfunction followed by delayed cell death in differentiated cortical neurons. *Sci. Rep.* **2018**, *8*, 14316. [[CrossRef](#)] [[PubMed](#)]
18. Koseoglu, M.M.; Norambuena, A.; Sharlow, E.R.; Lazo, J.S.; Bloom, G.S. Aberrant Neuronal Cell Cycle Re-Entry: The Pathological Confluence of Alzheimer's Disease and Brain Insulin Resistance, and Its Relation to Cancer. *J. Alzheimer's Dis.* **2019**, *67*, 1–11. [[CrossRef](#)]
19. Putzke, A.P.; Ventura, A.P.; Bailey, A.M.; Akture, C.; Opoku-Ansah, J.; Celiktas, M.; Hwang, M.S.; Darling, D.S.; Coleman, I.M.; Nelson, P.S.; et al. Metastatic progression of prostate cancer and e-cadherin regulation by zeb1 and SRC family kinases. *Am. J. Pathol.* **2011**, *179*, 400–410. [[CrossRef](#)]
20. Wu, Z.; Chang, P.C.; Yang, J.C.; Chu, C.Y.; Wang, L.Y.; Chen, N.T.; Ma, A.H.; Desai, S.J.; Lo, S.H.; Evans, C.P.; et al. Autophagy Blockade Sensitizes Prostate Cancer Cells towards Src Family Kinase Inhibitors. *Genes Cancer* **2010**, *1*, 40–49. [[CrossRef](#)]
21. Nam, J.S.; Ino, Y.; Sakamoto, M.; Hirohashi, S. Src family kinase inhibitor PP2 restores the E-cadherin/catenin cell adhesion system in human cancer cells and reduces cancer metastasis. *Clin. Cancer Res.* **2002**, *8*, 2430–2436. [[PubMed](#)]
22. Liu, D.; Sharp, F.R.; Van, K.C.; Ander, B.P.; Ghiasvand, R.; Zhan, X.; Stamova, B.; Jickling, G.C.; Lyeth, B.G. Inhibition of Src Family Kinases Protects Hippocampal Neurons and Improves Cognitive Function after Traumatic Brain Injury. *J. Neurotrauma* **2014**, *31*, 1268–1276. [[CrossRef](#)] [[PubMed](#)]
23. Liu, D.Z.; Cheng, X.Y.; Ander, B.P.; Xu, H.; Davis, R.R.; Gregg, J.P.; Sharp, F.R. Src kinase inhibition decreases thrombin-induced injury and cell cycle re-entry in striatal neurons. *Neurobiol. Dis.* **2008**, *30*, 201–211. [[CrossRef](#)] [[PubMed](#)]
24. Liu, D.Z.; Ander, B.P.; Xu, H.; Shen, Y.; Kaur, P.; Deng, W.; Sharp, F.R. Blood-brain barrier breakdown and repair by Src after thrombin-induced injury. *Ann. Neurol.* **2010**, *67*, 526–533. [[CrossRef](#)] [[PubMed](#)]
25. Berndt, N.; Karim, R.M.; Schonbrunn, E. Advances of small molecule targeting of kinases. *Curr. Opin. Chem. Biol.* **2017**, *39*, 126–132. [[CrossRef](#)]
26. Fabbro, D.; Cowan-Jacob, S.W.; Moebitz, H. Ten things you should know about protein kinases: IUPHAR Review 14. *Br. J. Pharmacol.* **2015**, *172*, 2675–2700. [[CrossRef](#)] [[PubMed](#)]
27. Vlastaridis, P.; Kyriakidou, P.; Chaliotis, A.; Van de Peer, Y.; Oliver, S.G.; Amoutzias, G.D. Estimating the total number of phosphoproteins and phosphorylation sites in eukaryotic proteomes. *Gigascience* **2017**, *6*, giw015. [[CrossRef](#)]
28. An, E.; Brognard, J. Orange is the new black: Kinases are the new master regulators of tumor suppression. *IUBMB Life* **2019**, *71*, 738–748. [[CrossRef](#)]
29. Du, Z.; Lovly, C.M. Mechanisms of receptor tyrosine kinase activation in cancer. *Mol. Cancer* **2018**, *17*, 58. [[CrossRef](#)]
30. Newton, A.C. Protein kinase C as a tumor suppressor. *Semin. Cancer Biol.* **2018**, *48*, 18–26. [[CrossRef](#)]
31. Vasterling, J.J.; Jacob, S.N.; Rasmusson, A. Traumatic Brain Injury and Posttraumatic Stress Disorder: Conceptual, Diagnostic, and Therapeutic Considerations in the Context of Co-Occurrence. *J. Neuropsychiatry Clin. Neurosci.* **2018**, *30*, 91–100. [[CrossRef](#)] [[PubMed](#)]
32. Bryant, R.A.; O'Donnell, M.L.; Creamer, M.; McFarlane, A.C.; Clark, C.R.; Silove, D. The psychiatric sequelae of traumatic injury. *Am. J. Psychiatry* **2010**, *167*, 312–320. [[CrossRef](#)] [[PubMed](#)]
33. Lindquist, L.K.; Love, H.C.; Elbogen, E.B. Traumatic Brain Injury in Iraq and Afghanistan Veterans: New Results From a National Random Sample Study. *J. Neuropsychiatry Clin. Neurosci.* **2017**, *29*, 254–259. [[CrossRef](#)] [[PubMed](#)]
34. Yang, Y.; Wang, C.; Xiang, Y.; Lu, J.; Penzel, T. Editorial: Mental Disorders Associated With Neurological Diseases. *Front. Psychiatry* **2020**, *11*, 196. [[CrossRef](#)] [[PubMed](#)]
35. Dewan, M.C.; Rattani, A.; Gupta, S.; Baticulon, R.E.; Hung, Y.C.; Punchak, M.; Agrawal, A.; Adeleye, A.O.; Shrivastava, M.G.; Rubiano, A.M.; et al. Estimating the global incidence of traumatic brain injury. *J. Neurosurg.* **2018**, *130*, 1080–1097. [[CrossRef](#)]
36. Royce, M.; Osgood, C.; Mulkey, F.; Bloomquist, E.; Pierce, W.F.; Roy, A.; Kalavar, S.; Ghosh, S.; Philip, R.; Rizvi, F.; et al. FDA Approval Summary: Abemaciclib With Endocrine Therapy for High-Risk Early Breast Cancer. *J. Clin. Oncol.* **2022**, *40*, 1155–1162. [[CrossRef](#)]
37. Schadendorf, D.; Fisher, D.E.; Garbe, C.; Gershenwald, J.E.; Grob, J.J.; Halpern, A.; Herlyn, M.; Marchetti, M.A.; McArthur, G.; Ribas, A.; et al. Melanoma. *Nat. Rev. Dis. Primers* **2015**, *1*, 15003. [[CrossRef](#)]
38. Lonskaya, I.; Hebron, M.L.; Desforgues, N.M.; Franjie, A.; Moussa, C.E. Tyrosine kinase inhibition increases functional parkin-Beclin-1 interaction and enhances amyloid clearance and cognitive performance. *EMBO Mol. Med.* **2013**, *5*, 1247–1262. [[CrossRef](#)]
39. Lonskaya, I.; Hebron, M.L.; Selby, S.T.; Turner, R.S.; Moussa, C.E. Nilotinib and bosutinib modulate pre-plaque alterations of blood immune markers and neuro-inflammation in Alzheimer's disease models. *Neuroscience* **2015**, *304*, 316–327. [[CrossRef](#)]
40. Hebron, M.L.; Lonskaya, I.; Olopade, P.; Selby, S.T.; Pagan, F.; Moussa, C.E. Tyrosine Kinase Inhibition Regulates Early Systemic Immune Changes and Modulates the Neuroimmune Response in  $\alpha$ -Synucleinopathy. *J. Clin. Cell Immunol.* **2014**, *5*, 259. [[CrossRef](#)]
41. Hebron, M.L.; Javidnia, M.; Moussa, C.E. Tau clearance improves astrocytic function and brain glutamate-glutamine cycle. *J. Neurol. Sci.* **2018**, *391*, 90–99. [[CrossRef](#)] [[PubMed](#)]
42. Lonskaya, I.; Desforgues, N.M.; Hebron, M.L.; Moussa, C.E. Ubiquitination increases parkin activity to promote autophagic  $\alpha$ -synuclein clearance. *PLoS ONE* **2013**, *8*, e83914. [[CrossRef](#)] [[PubMed](#)]



43. Huang, X.Y.; Hu, Q.P.; Shi, H.Y.; Zheng, Y.Y.; Hu, R.R.; Guo, Q. Everolimus inhibits PI3K/Akt/mTOR and NF- $\kappa$ B/IL-6 signaling and protects seizure-induced brain injury in rats. *J. Chem. Neuroanat.* **2021**, *114*, 101960. [[CrossRef](#)] [[PubMed](#)]
44. Yang, M.T.; Lin, Y.C.; Ho, W.H.; Liu, C.L.; Lee, W.T. Everolimus is better than rapamycin in attenuating neuroinflammation in kainic acid-induced seizures. *J. Neuroinflamm.* **2017**, *14*, 15. [[CrossRef](#)] [[PubMed](#)]
45. Jousen, A.M.; Wolf, S.; Kaiser, P.K.; Boyer, D.; Schmelter, T.; Sandbrink, R.; Zeitz, O.; Deeg, G.; Richter, A.; Zimmermann, T.; et al. The Developing Regorafenib Eye drops for neovascular Age-related Macular degeneration (DREAM) study: An open-label phase II trial. *Br. J. Clin. Pharmacol.* **2019**, *85*, 347–355. [[CrossRef](#)] [[PubMed](#)]
46. Wang, F.; Li, S.; Wang, T.Y.; Lopez, G.A.; Antoshechkin, I.; Chou, T.F. P97/VCP ATPase inhibitors can rescue p97 mutation-linked motor neuron degeneration. *Brain Commun.* **2022**, *4*, fcac176. [[CrossRef](#)] [[PubMed](#)]
47. Wang, X.; Ma, L.; Li, J.; Kong, F. Activated cell-cycle CDK4/CyclinD1-pRB-E2F1 signaling pathway is involved in the apoptosis of dorsal raphe nucleus in the rat model of PTSD. *Biochem. Biophys. Res. Commun.* **2022**, *602*, 142–148. [[CrossRef](#)] [[PubMed](#)]
48. Chen, Y.J.; Hsu, C.C.; Shiao, Y.J.; Wang, H.T.; Lo, Y.L.; Lin, A.M.Y. Anti-inflammatory effect of afatinib (an EGFR-TKI) on OGD-induced neuroinflammation. *Sci. Rep.* **2019**, *9*, 2516. [[CrossRef](#)]
49. Linnerbauer, M.; Löfflein, L.; Vandrey, O.; Tsaktanis, T.; Beer, A.; Naumann, U.J.; Panier, F.; Beyer, T.; Nirschl, L.; Kuramatsu, J.B.; et al. Intranasal delivery of a small-molecule ErbB inhibitor promotes recovery from acute and late-stage CNS inflammation. *JCI Insight* **2022**, *7*, e154824. [[CrossRef](#)]
50. Turner, J.R.; Ray, R.; Lee, B.; Everett, L.; Xiang, J.; Jepson, C.; Kaestner, K.H.; Lerman, C.; Blendy, J.A. Evidence from mouse and man for a role of neuregulin 3 in nicotine dependence. *Mol. Psychiatry* **2014**, *19*, 801–810. [[CrossRef](#)]
51. Singh, C.S.B.; Choi, K.B.; Munro, L.; Wang, H.Y.; Pfeifer, C.G.; Jefferies, W.A. Reversing pathology in a preclinical model of Alzheimer’s disease by hacking cerebrovascular neoangiogenesis with advanced cancer therapeutics. *EBioMedicine* **2021**, *71*, 103503. [[CrossRef](#)] [[PubMed](#)]
52. Dutton, J.W., 3rd; Chen, H.; You, C.; Brodie, M.S.; Lasek, A.W. Anaplastic lymphoma kinase regulates binge-like drinking and dopamine receptor sensitivity in the ventral tegmental area. *Addict. Biol.* **2017**, *22*, 665–678. [[CrossRef](#)] [[PubMed](#)]
53. Hamada, K.; Ferguson, L.B.; Mayfield, R.D.; Krishnan, H.R.; Maienschein-Cline, M.; Lasek, A.W. Binge-like ethanol drinking activates anaplastic lymphoma kinase signaling and increases the expression of STAT3 target genes in the mouse hippocampus and prefrontal cortex. *Genes Brain Behav.* **2021**, *20*, e12729. [[CrossRef](#)]
54. Gavegnano, C.; Haile, W.B.; Hurwitz, S.; Tao, S.; Jiang, Y.; Schinazi, R.F.; Tyor, W.R. Baricitinib reverses HIV-associated neurocognitive disorders in a SCID mouse model and reservoir seeding in vitro. *J. Neuroinflamm.* **2019**, *16*, 182. [[CrossRef](#)]
55. Nakamura, J.; Yanagida, M.; Saito, K.; Kamata, Y.; Nagashima, T.; Iwamoto, M.; Sato, T.; Sato, K. Epstein-Barr Virus Encephalitis in a Patient with Rheumatoid Arthritis. *Mod. Rheumatol. Case Rep.* **2021**, *6*, 160–162. [[CrossRef](#)]
56. Dang, C.; Lu, Y.; Chen, X.; Li, Q. Baricitinib Ameliorates Experimental Autoimmune Encephalomyelitis by Modulating the Janus Kinase/Signal Transducer and Activator of Transcription Signaling Pathway. *Front. Immunol.* **2021**, *12*, 650708. [[CrossRef](#)]
57. Tuttle, K.D.; Waugh, K.A.; Araya, P.; Minter, R.; Orlicky, D.J.; Ludwig, M.; Andrysik, Z.; Burchill, M.A.; Tamburini, B.A.J.; Sempeck, C.; et al. JAK1 Inhibition Blocks Lethal Immune Hypersensitivity in a Mouse Model of Down Syndrome. *Cell Rep.* **2020**, *33*, 108407. [[CrossRef](#)] [[PubMed](#)]
58. Zheng, X.Q.; Huang, J.F.; Lin, J.L.; Zhu, Y.X.; Wang, M.Q.; Guo, M.L.; Zan, X.J.; Wu, A.M. Controlled release of baricitinib from a thermos-responsive hydrogel system inhibits inflammation by suppressing JAK2/STAT3 pathway in acute spinal cord injury. *Colloids Surf. B Biointerfaces* **2021**, *199*, 111532. [[CrossRef](#)]
59. Liu, C.; Arnold, R.; Henriques, G.; Djabali, K. Inhibition of JAK-STAT Signaling with Baricitinib Reduces Inflammation and Improves Cellular Homeostasis in Progeria Cells. *Cells* **2019**, *8*, 1276. [[CrossRef](#)]
60. Agarwal, K.; Katare, D.P.; Jakhmola-Mani, R. Foresee novel targets for Alzheimer’s disease by investigating repurposed drugs. *CNS Neurol. Disord. Drug Targets*, 2022; online ahead of print. [[CrossRef](#)]
61. Schapansky, J.; Grinberg, Y.Y.; Osiecki, D.M.; Freeman, E.A.; Walker, S.G.; Karran, E.; Gopalakrishnan, S.M.; Talanian, R.V. MEK1/2 activity modulates TREM2 cell surface recruitment. *J. Biol. Chem.* **2021**, *296*, 100218. [[CrossRef](#)]
62. Ma, L.; Manaenko, A.; Ou, Y.B.; Shao, A.W.; Yang, S.X.; Zhang, J.H. Bosutinib Attenuates Inflammation via Inhibiting Salt-Inducible Kinases in Experimental Model of Intracerebral Hemorrhage on Mice. *Stroke* **2017**, *48*, 3108–3116. [[CrossRef](#)] [[PubMed](#)]
63. Liang, S.; Pong, K.; Gonzales, C.; Chen, Y.; Ling, H.P.; Mark, R.J.; Boschelli, F.; Boschelli, D.H.; Ye, F.; Barrios Sosa, A.C.; et al. Neuroprotective profile of novel SRC kinase inhibitors in rodent models of cerebral ischemia. *J. Pharmacol. Exp. Ther.* **2009**, *331*, 827–835. [[CrossRef](#)] [[PubMed](#)]
64. Wenqiang, C.; Lonskaya, I.; Hebron, M.L.; Ibrahim, Z.; Olszewski, R.T.; Neale, J.H.; Moussa, C.E. Parkin-mediated reduction of nuclear and soluble TDP-43 reverses behavioral decline in symptomatic mice. *Hum. Mol. Genet.* **2014**, *23*, 4960–4969. [[CrossRef](#)] [[PubMed](#)]
65. Heyburn, L.; Hebron, M.L.; Smith, J.; Winston, C.; Bechara, J.; Li, Z.; Lonskaya, I.; Burns, M.P.; Harris, B.T.; Moussa, C.E. Tyrosine kinase inhibition reverses TDP-43 effects on synaptic protein expression, astrocytic function and amino acid dis-homeostasis. *J. Neurochem.* **2016**, *139*, 610–623. [[CrossRef](#)]
66. Yilmaz, S.; Alkan, T.; Ballar Kirmizibayrak, P. A new underlying mechanism for the neuroprotective effect of bosutinib: Reverting toxicity-induced PARYlation in SIN1-mediated neurotoxicity. *J. Biochem. Mol. Toxicol.* **2021**, *35*, e22915. [[CrossRef](#)]



67. Kiris, E.; Burnett, J.C.; Nuss, J.E.; Wanner, L.M.; Peyser, B.D.; Du, H.T.; Gomba, G.Y.; Kota, K.P.; Panchal, R.G.; Gussio, R.; et al. SRC family kinase inhibitors antagonize the toxicity of multiple serotypes of botulinum neurotoxin in human embryonic stem cell-derived motor neurons. *Neurotox. Res.* **2015**, *27*, 384–398. [[CrossRef](#)]
68. Tang, X.; Drotar, J.; Li, K.; Clairmont, C.D.; Brumm, A.S.; Sullins, A.J.; Wu, H.; Liu, X.S.; Wang, J.; Gray, N.S.; et al. Pharmacological enhancement of KCC2 gene expression exerts therapeutic effects on human Rett syndrome neurons and Mecp2 mutant mice. *Sci. Transl. Med.* **2019**, *11*, eaau0164. [[CrossRef](#)]
69. Tucker Edmister, S.; Del Rosario Hernández, T.; Ibrahim, R.; Brown, C.A.; Gore, S.V.; Kakodkar, R.; Kreiling, J.A.; Creton, R. Novel use of FDA-approved drugs identified by cluster analysis of behavioral profiles. *Sci. Rep.* **2022**, *12*, 6120. [[CrossRef](#)]
70. Bolz, S.N.; Salentin, S.; Jennings, G.; Haupt, V.J.; Sternecker, J.; Schroeder, M. Structural binding site comparisons reveal Crizotinib as a novel LRRK2 inhibitor. *Comput. Struct. Biotechnol. J.* **2021**, *19*, 3674–3681. [[CrossRef](#)]
71. Lim, J.W.; Kim, S.K.; Choi, S.Y.; Kim, D.H.; Gadhe, C.G.; Lee, H.N.; Kim, H.J.; Kim, J.; Cho, S.J.; Hwang, H.; et al. Identification of crizotinib derivatives as potent SHIP2 inhibitors for the treatment of Alzheimer's disease. *Eur. J. Med. Chem.* **2018**, *157*, 405–422. [[CrossRef](#)]
72. Defaye, M.; Iftinca, M.C.; Gadotti, V.M.; Basso, L.; Abdullah, N.S.; Cuména, M.; Agosti, F.; Hassan, A.; Flynn, R.; Martin, J.; et al. The neuronal tyrosine kinase receptor ligand ALKAL2 mediates persistent pain. *J. Clin. Invest.* **2022**, *132*, e154317. [[CrossRef](#)] [[PubMed](#)]
73. Yang, Z.; Ahn, H.J.; Nam, H.W. Gefitinib inhibits the growth of *Toxoplasma gondii* in HeLa cells. *Korean J. Parasitol.* **2014**, *52*, 439–441. [[CrossRef](#)] [[PubMed](#)]
74. Camp, E.; Anderson, P.J.; Zannettino, A.C.W.; Glackin, C.A.; Gronthos, S. Tyrosine kinase receptor c-ros-oncogene 1 inhibition alleviates aberrant bone formation of TWIST-1 haploinsufficient calvarial cells from Saethre-Chotzen syndrome patients. *J. Cell Physiol.* **2018**, *233*, 7320–7332. [[CrossRef](#)] [[PubMed](#)]
75. Cruz, S.A.; Qin, Z.; Stewart, A.F.R.; Chen, H.H. Dabrafenib, an inhibitor of RIP3 kinase-dependent necroptosis, reduces ischemic brain injury. *Neural Regen. Res.* **2018**, *13*, 252–256. [[CrossRef](#)]
76. Sugaya, T.; Kanno, H.; Matsuda, M.; Handa, K.; Tateda, S.; Murakami, T.; Ozawa, H.; Itoi, E. B-RAF(V600E) Inhibitor Dabrafenib Attenuates RIPK3-Mediated Necroptosis and Promotes Functional Recovery after Spinal Cord Injury. *Cells* **2019**, *8*, 1582. [[CrossRef](#)]
77. Uenaka, T.; Satake, W.; Cha, P.C.; Hayakawa, H.; Baba, K.; Jiang, S.; Kobayashi, K.; Kanagawa, M.; Okada, Y.; Mochizuki, H.; et al. In silico drug screening by using genome-wide association study data repurposed dabrafenib, an anti-melanoma drug, for Parkinson's disease. *Hum. Mol. Genet.* **2018**, *27*, 3974–3985. [[CrossRef](#)]
78. Okamoto, T. Parkinson's Disease: Amantadine, zonisamide, dabrafenib. *Brain Nerve* **2019**, *71*, 953–959. [[CrossRef](#)]
79. Elkouzi, A.; Rauschkolb, P.; Grogg, K.L.; Gilchrist, J.M. Neurohistiocytosis of the Cerebellum: A Rare Cause of Ataxia. *Mov. Disord. Clin. Pract.* **2016**, *3*, 125–129. [[CrossRef](#)]
80. Yu, W.; Parakramaweera, R.; Teng, S.; Gowda, M.; Sharad, Y.; Thakker-Varia, S.; Alder, J.; Sesti, F. Oxidation of KCNB1 Potassium Channels Causes Neurotoxicity and Cognitive Impairment in a Mouse Model of Traumatic Brain Injury. *J. Neurosci.* **2016**, *36*, 11084–11096. [[CrossRef](#)]
81. Saminathan, H.; Charli, A.; Luo, J.; Panicker, N.; Gordon, R.; Hostetter, J.M.; Jin, H.; Anantharam, V.; Kanthasamy, A.G.; Kanthasamy, A. Fyn kinase mediates pro-inflammatory response in a mouse model of endotoxemia: Relevance to translational research. *Eur. J. Pharmacol.* **2020**, *881*, 173259. [[CrossRef](#)]
82. Gangoso, E.; Talaverón, R.; Jaraíz-Rodríguez, M.; Domínguez-Prieto, M.; Ezan, P.; Koulakoff, A.; Medina, J.M.; Giaume, C.; Taberner, A. A c-Src Inhibitor Peptide Based on Connexin43 Exerts Neuroprotective Effects through the Inhibition of Glial Hemichannel Activity. *Front. Mol. Neurosci.* **2017**, *10*, 418. [[CrossRef](#)] [[PubMed](#)]
83. El-Nimri, N.W.; Moore, S.M.; Zangwill, L.M.; Proudfoot, J.A.; Weinreb, R.N.; Skowronska-Krawczyk, D.; Baxter, S.L. Evaluating the neuroprotective impact of senolytic drugs on human vision. *Sci. Rep.* **2020**, *10*, 21752. [[CrossRef](#)] [[PubMed](#)]
84. Musi, N.; Valentine, J.M.; Sickora, K.R.; Baeuerle, E.; Thompson, C.S.; Shen, Q.; Orr, M.E. Tau protein aggregation is associated with cellular senescence in the brain. *Aging Cell* **2018**, *17*, e12840. [[CrossRef](#)] [[PubMed](#)]
85. Azizi, G.; Goudarzvand, M.; Afraei, S.; Sedaghat, R.; Mirshafiey, A. Therapeutic effects of dasatinib in mouse model of multiple sclerosis. *Immunopharmacol. Immunotoxicol.* **2015**, *37*, 287–294. [[CrossRef](#)] [[PubMed](#)]
86. Katsumata, R.; Ishigaki, S.; Katsuno, M.; Kawai, K.; Sone, J.; Huang, Z.; Adachi, H.; Tanaka, F.; Urano, F.; Sobue, G. c-Abl inhibition delays motor neuron degeneration in the G93A mouse, an animal model of amyotrophic lateral sclerosis. *PLoS ONE* **2012**, *7*, e46185. [[CrossRef](#)] [[PubMed](#)]
87. Lawana, V.; Singh, N.; Sarkar, S.; Charli, A.; Jin, H.; Anantharam, V.; Kanthasamy, A.G.; Kanthasamy, A. Involvement of c-Abl Kinase in Microglial Activation of NLRP3 Inflammasome and Impairment in Autolysosomal System. *J. Neuroimmune Pharmacol.* **2017**, *12*, 624–660. [[CrossRef](#)] [[PubMed](#)]
88. Torres, P.; Anerillas, C.; Ramírez-Núñez, O.; Fernández, A.; Encinas, M.; Povedano, M.; Andrés-Benito, P.; Ferrer, I.; Ayala, V.; Pamplona, R.; et al. A motor neuron disease mouse model reveals a non-canonical profile of senescence biomarkers. *Dis. Models Mech.* **2022**, *15*, dmm049059. [[CrossRef](#)]
89. Ya, J.; Kadir, R.R.A.; Bayraktutan, U. Delay of endothelial cell senescence protects cerebral barrier against age-related dysfunction: Role of senolytics and senomorphics. *Tissue Barriers*, 2022; *online ahead of print*. [[CrossRef](#)]

90. Krzystyniak, A.; Wesierska, M.; Petrazzo, G.; Gadecka, A.; Dudkowska, M.; Bielak-Zmijewska, A.; Mosieniak, G.; Figiel, I.; Wlodarczyk, J.; Sikora, E. Combination of dasatinib and quercetin improves cognitive abilities in aged male Wistar rats, alleviates inflammation and changes hippocampal synaptic plasticity and histone H3 methylation profile. *Aging Albany NY* **2022**, *14*, 572–595. [[CrossRef](#)]
91. Ogrodnik, M.; Zhu, Y.; Langhi, L.G.P.; Tchkonja, T.; Krüger, P.; Fielder, E.; Victorelli, S.; Ruswhandi, R.A.; Giorgadze, N.; Pirtskhalava, T.; et al. Obesity-Induced Cellular Senescence Drives Anxiety and Impairs Neurogenesis. *Cell Metab.* **2019**, *29*, 1061–1077.e8. [[CrossRef](#)]
92. Lin, Y.F.; Wang, L.Y.; Chen, C.S.; Li, C.C.; Hsiao, Y.H. Cellular senescence as a driver of cognitive decline triggered by chronic unpredictable stress. *Neurobiol. Stress* **2021**, *15*, 100341. [[CrossRef](#)]
93. Wang, D.; Howell, B.W.; Olson, E.C. Maternal Ethanol Exposure Acutely Elevates Src Family Kinase Activity in the Fetal Cortex. *Mol. Neurobiol.* **2021**, *58*, 5210–5223. [[CrossRef](#)] [[PubMed](#)]
94. Koprivica, V.; Cho, K.S.; Park, J.B.; Yiu, G.; Atwal, J.; Gore, B.; Kim, J.A.; Lin, E.; Tessier-Lavigne, M.; Chen, D.F.; et al. EGFR activation mediates inhibition of axon regeneration by myelin and chondroitin sulfate proteoglycans. *Science* **2005**, *310*, 106–110. [[CrossRef](#)] [[PubMed](#)]
95. Luo, Y.; Tang, H.; Zhang, Z.; Zhao, R.; Wang, C.; Hou, W.; Huang, Q.; Liu, J. Pharmacological inhibition of epidermal growth factor receptor attenuates intracranial aneurysm formation by modulating the phenotype of vascular smooth muscle cells. *CNS Neurosci. Ther.* **2022**, *28*, 64–76. [[CrossRef](#)] [[PubMed](#)]
96. LePichon, C.E.; Dominguez, S.L.; Solanoy, H.; Ngu, H.; Lewin-Koh, N.; Chen, M.; Eastham-Anderson, J.; Watts, R.; Scarce-Levie, K. EGFR inhibitor erlotinib delays disease progression but does not extend survival in the SOD1 mouse model of ALS. *PLoS ONE* **2013**, *8*, e62342. [[CrossRef](#)]
97. Pan, P.; Dobrowsky, R.T. Differential expression of neuregulin-1 isoforms and downregulation of erbin are associated with Erb B2 receptor activation in diabetic peripheral neuropathy. *Acta Neuropathol. Commun.* **2013**, *1*, 39. [[CrossRef](#)]
98. McGuire, J.F.; Rouen, S.; Siegfried, E.; Wright, D.E.; Dobrowsky, R.T. Caveolin-1 and altered neuregulin signaling contribute to the pathophysiological progression of diabetic peripheral neuropathy. *Diabetes* **2009**, *58*, 2677–2686. [[CrossRef](#)]
99. Wang, L.; Chiang, H.C.; Wu, W.; Liang, B.; Xie, Z.; Yao, X.; Ma, W.; Du, S.; Zhong, Y. Epidermal growth factor receptor is a preferred target for treating amyloid- $\beta$ -induced memory loss. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 16743–16748. [[CrossRef](#)]
100. Lechpammer, M.; Tran, Y.P.; Wintermark, P.; Martínez-Cerdeño, V.; Krishnan, V.V.; Ahmed, W.; Berman, R.F.; Jensen, F.E.; Nudler, E.; Zagzag, D. Upregulation of cystathionine  $\beta$ -synthase and p70S6K/S6 in neonatal hypoxic ischemic brain injury. *Brain Pathol.* **2017**, *27*, 449–458. [[CrossRef](#)]
101. Kurdi, A.; Roth, L.; Van der Veken, B.; Van Dam, D.; De Deyn, P.P.; De Doncker, M.; Neels, H.; De Meyer, G.R.Y.; Martinet, W. Everolimus depletes plaque macrophages, abolishes intraplaque neovascularization and improves survival in mice with advanced atherosclerosis. *Vasc. Pharmacol.* **2019**, *113*, 70–76. [[CrossRef](#)]
102. Li, D.; Wang, C.; Yao, Y.; Chen, L.; Liu, G.; Zhang, R.; Liu, Q.; Shi, F.D.; Hao, J. mTORC1 pathway disruption ameliorates brain inflammation following stroke via a shift in microglia phenotype from M1 type to M2 type. *FASEB J.* **2016**, *30*, 3388–3399. [[CrossRef](#)]
103. Suvanish Kumar, V.S.; Pretorius, E.; Rajanikant, G.K. The Synergistic Combination of Everolimus and Paroxetine Exerts Post-ischemic Neuroprotection In Vitro. *Cell Mol. Neurobiol.* **2018**, *38*, 1383–1397. [[CrossRef](#)] [[PubMed](#)]
104. Forouzanfar, F.; Ebrahimi, P.R.; Sadeghnia, H.R. Neuroprotection of Everolimus Against Focal Cerebral Ischemia-Reperfusion Injury in Rats. *J. Stroke Cerebrovasc. Dis.* **2022**, *31*, 106576. [[CrossRef](#)] [[PubMed](#)]
105. Cassano, T.; Magini, A.; Giovagnoli, S.; Polchi, A.; Calcagnini, S.; Pace, L.; Lavecchia, M.A.; Scuderi, C.; Bronzuoli, M.R.; Ruggeri, L.; et al. Early intrathecal infusion of everolimus restores cognitive function and mood in a murine model of Alzheimer’s disease. *Exp. Neurol.* **2019**, *311*, 88–105. [[CrossRef](#)] [[PubMed](#)]
106. Fanoudi, S.; Hosseini, M.; Alavi, M.S.; Boroushaki, M.T.; Hosseini, A.; Sadeghnia, H.R. Everolimus, a mammalian target of rapamycin inhibitor, ameliorated streptozotocin-induced learning and memory deficits via neurochemical alterations in male rats. *EXCLI J.* **2018**, *17*, 999–1017. [[CrossRef](#)] [[PubMed](#)]
107. Roscic, A.; Baldo, B.; Crochemore, C.; Marcellin, D.; Paganetti, P. Induction of autophagy with catalytic mTOR inhibitors reduces huntingtin aggregates in a neuronal cell model. *J. Neurochem.* **2011**, *119*, 398–407. [[CrossRef](#)] [[PubMed](#)]
108. Fox, J.H.; Connor, T.; Chopra, V.; Dorsey, K.; Kama, J.A.; Bleckmann, D.; Betschart, C.; Hoyer, D.; Frentzel, S.; Difiglia, M.; et al. The mTOR kinase inhibitor Everolimus decreases S6 kinase phosphorylation but fails to reduce mutant huntingtin levels in brain and is not neuroprotective in the R6/2 mouse model of Huntington’s disease. *Mol. Neurodegener.* **2010**, *5*, 26. [[CrossRef](#)]
109. Chen, L.; Zhang, Y.; Li, D.; Zhang, N.; Liu, R.; Han, B.; Wei, C.; Liu, H.; Xu, X.; Hao, J. Everolimus (RAD001) ameliorates vascular cognitive impairment by regulating microglial function via the mTORC1 signaling pathway. *J. Neuroimmunol.* **2016**, *299*, 164–171. [[CrossRef](#)] [[PubMed](#)]
110. Dello Russo, C.; Lisi, L.; Tringali, G.; Navarra, P. Involvement of mTOR kinase in cytokine-dependent microglial activation and cell proliferation. *Biochem. Pharmacol.* **2009**, *78*, 1242–1251. [[CrossRef](#)]
111. Bansal, S.; Agrawal, M.; Mahendiratta, S.; Kumar, S.; Arora, S.; Joshi, R.; Prajapat, M.; Sarma, P.; Prakash, A.; Chopra, K.; et al. Everolimus: A potential therapeutic agent targeting PI3K/Akt pathway in brain insulin system dysfunction and associated neurobehavioral deficits. *Fundam. Clin. Pharmacol.* **2021**, *35*, 1018–1031. [[CrossRef](#)]

112. Alavi, M.S.; Fanoudi, S.; Hosseini, A.; Jalili-Nik, M.; Bagheri, A.; Sadeghnia, H.R. Everolimus attenuates glutamate-induced PC12 cells death. *Int. J. Neurosci.* **2021**, *17*, 1–12. [[CrossRef](#)]
113. Han, R.; Gao, J.; Zhai, H.; Xiao, J.; Ding, Y.; Hao, J. RAD001 (everolimus) attenuates experimental autoimmune neuritis by inhibiting the mTOR pathway, elevating Akt activity and polarizing M2 macrophages. *Exp. Neurol.* **2016**, *280*, 106–114. [[CrossRef](#)] [[PubMed](#)]
114. Hoepner, R.; Bagnoud, M.; Pistor, M.; Salmen, A.; Briner, M.; Synn, H.; Schrewe, L.; Guse, K.; Ahmadi, F.; Demir, S.; et al. Vitamin D increases glucocorticoid efficacy via inhibition of mTORC1 in experimental models of multiple sclerosis. *Acta Neuropathol.* **2019**, *138*, 443–456. [[CrossRef](#)] [[PubMed](#)]
115. Schneider, M.; de Vries, P.J.; Schönig, K.; Rößner, V.; Waltereit, R. mTOR inhibitor reverses autistic-like social deficit behaviours in adult rats with both Tsc2 haploinsufficiency and developmental status epilepticus. *Eur. Arch. Psychiatry Clin. Neurosci.* **2017**, *267*, 455–463. [[CrossRef](#)] [[PubMed](#)]
116. Petrasek, T.; Vojtechova, I.; Klovra, O.; Tuckova, K.; Vejmla, C.; Rak, J.; Sulakova, A.; Kaping, D.; Bernhardt, N.; de Vries, P.J.; et al. mTOR inhibitor improves autistic-like behaviors related to Tsc2 haploinsufficiency but not following developmental status epilepticus. *J. Neurodev. Disord.* **2021**, *13*, 14. [[CrossRef](#)]
117. Mishra, N.; Wang, P.; Goldsmith, D.; Zhao, X.; Xue, Y.; Christians, U.; Minassian, B.A. Everolimus does not prevent Lafora body formation in murine Lafora disease. *Neurol. Genet.* **2017**, *3*, e127. [[CrossRef](#)]
118. Tao, P.; Jing, Z.; Shou-Hong, G.; Shu-Juan, P.; Jian-Peng, J.; Wen-Quan, L.; Wan-Sheng, C. Effects of leptin on norepinephrine in acute ischemic stroke. *Pharmazie* **2019**, *74*, 477–480. [[CrossRef](#)]
119. Yue, X.; Liu, L.; Yan, H.; Gui, Y.; Zhao, J.; Zhang, P. Intracerebral Hemorrhage Induced Brain Injury Is Mediated by the Interleukin-12 Receptor in Rats. *Neuropsychiatr. Dis. Treat.* **2020**, *16*, 891–900. [[CrossRef](#)]
120. Zhang, Q.; Zhang, Y.; Diamond, S.; Boer, J.; Harris, J.J.; Li, Y.; Rupa, M.; Behshad, E.; Gardiner, C.; Collier, P.; et al. The Janus kinase 2 inhibitor fedratinib inhibits thiamine uptake: A putative mechanism for the onset of Wernicke’s encephalopathy. *Drug Metab. Dispos.* **2014**, *42*, 1656–1662. [[CrossRef](#)]
121. Hazell, A.S.; Afadl, S.; Cheres, D.A.; Azar, A. Treatment of rats with the JAK-2 inhibitor fedratinib does not lead to experimental Wernicke’s encephalopathy. *Neurosci. Lett.* **2017**, *642*, 163–167. [[CrossRef](#)]
122. Zhou, Y.; Li, C.; Li, D.; Zheng, Y.; Wang, J. IL-5 blocks apoptosis and tau hyperphosphorylation induced by A $\beta$ (25–35) peptide in PC12 cells. *J. Physiol. Biochem.* **2017**, *73*, 259–266. [[CrossRef](#)]
123. Xue, W.; Zhao, Y.; Xiao, Z.; Wu, X.; Ma, D.; Han, J.; Li, X.; Xue, X.; Yang, Y.; Fang, Y.; et al. Epidermal growth factor receptor-extracellular-regulated kinase blockade upregulates TRIM32 signaling cascade and promotes neurogenesis after spinal cord injury. *Stem Cells* **2020**, *38*, 118–133. [[CrossRef](#)] [[PubMed](#)]
124. Mizuno, M.; Sotoyama, H.; Namba, H.; Shibuya, M.; Eda, T.; Wang, R.; Okubo, T.; Nagata, K.; Iwakura, Y.; Nawa, H. ErbB inhibitors ameliorate behavioral impairments of an animal model for schizophrenia: Implication of their dopamine-modulatory actions. *Transl. Psychiatry* **2013**, *3*, e252. [[CrossRef](#)] [[PubMed](#)]
125. Zheng, Y.; Shang, F.; An, L.; Zhao, H.; Liu, X. NOD2-RIP2 contributes to the inflammatory responses of mice in vivo to *Streptococcus pneumoniae*. *Neurosci. Lett.* **2018**, *671*, 43–49. [[CrossRef](#)] [[PubMed](#)]
126. Lopez Corcino, Y.; Gonzalez Ferrer, S.; Mantilla, L.E.; Trikeriotis, S.; Yu, J.S.; Kim, S.; Hansen, S.; Portillo, J.C.; Subauste, C.S. *Toxoplasma gondii* induces prolonged host epidermal growth factor receptor signalling to prevent parasite elimination by autophagy: Perspectives for in vivo control of the parasite. *Cell Microbiol.* **2019**, *21*, e13084. [[CrossRef](#)]
127. Ito, M.; Shichita, T.; Okada, M.; Komine, R.; Noguchi, Y.; Yoshimura, A.; Morita, R. Bruton’s tyrosine kinase is essential for NLRP3 inflammasome activation and contributes to ischaemic brain injury. *Nat. Commun.* **2015**, *6*, 7360. [[CrossRef](#)]
128. Jin, L.; Mo, Y.; Yue, E.L.; Liu, Y.; Liu, K.Y. Ibrutinib ameliorates cerebral ischemia/reperfusion injury through autophagy activation and PI3K/Akt/mTOR signaling pathway in diabetic mice. *Bioengineered* **2021**, *12*, 7432–7445. [[CrossRef](#)]
129. Yu, C.G.; Bondada, V.; Iqbal, H.; Moore, K.L.; Gensel, J.C.; Bondada, S.; Geddes, J.W. Inhibition of Bruton Tyrosine Kinase Reduces Neuroimmune Cascade and Promotes Recovery after Spinal Cord Injury. *Int. J. Mol. Sci.* **2021**, *23*, 355. [[CrossRef](#)]
130. Torabi, S.; Anjamrooz, S.H.; Zeraatpisheh, Z.; Aligholi, H.; Azari, H. Ibrutinib reduces neutrophil infiltration, preserves neural tissue and enhances locomotor recovery in mouse contusion model of spinal cord injury. *Anat. Cell Biol.* **2021**, *54*, 350–360. [[CrossRef](#)]
131. Ekpenyong-Akiba, A.E.; Poblocka, M.; Althubiti, M.; Rada, M.; Jurk, D.; Germano, S.; Kocsis-Fodor, G.; Shi, Y.; Canales, J.J.; Macip, S. Amelioration of age-related brain function decline by Bruton’s tyrosine kinase inhibition. *Aging Cell* **2020**, *19*, e13079. [[CrossRef](#)]
132. Lee, H.J.; Jeon, S.G.; Kim, J.; Kang, R.J.; Kim, S.M.; Han, K.M.; Park, H.; Kim, K.T.; Sung, Y.M.; Nam, H.Y.; et al. Ibrutinib modulates A $\beta$ /tau pathology, neuroinflammation, and cognitive function in mouse models of Alzheimer’s disease. *Aging Cell* **2021**, *20*, e13332. [[CrossRef](#)]
133. Keaney, J.; Gasser, J.; Gillet, G.; Scholz, D.; Kadiu, I. Inhibition of Bruton’s Tyrosine Kinase Modulates Microglial Phagocytosis: Therapeutic Implications for Alzheimer’s Disease. *J. Neuroimmune Pharmacol.* **2019**, *14*, 448–461. [[CrossRef](#)] [[PubMed](#)]
134. Nam, H.Y.; Nam, J.H.; Yoon, G.; Lee, J.Y.; Nam, Y.; Kang, H.J.; Cho, H.J.; Kim, J.; Hoe, H.S. Ibrutinib suppresses LPS-induced neuroinflammatory responses in BV2 microglial cells and wild-type mice. *J. Neuroinflamm.* **2018**, *15*, 271. [[CrossRef](#)] [[PubMed](#)]
135. Ghosh, S.; Mohammed, Z.; Singh, I. Bruton’s tyrosine kinase drives neuroinflammation and anxiogenic behavior in mouse models of stress. *J. Neuroinflamm.* **2021**, *18*, 289. [[CrossRef](#)] [[PubMed](#)]



136. Li, W.; Ali, T.; He, K.; Liu, Z.; Shah, F.A.; Ren, Q.; Liu, Y.; Jiang, A.; Li, S. Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. *Brain Behav. Immun.* **2021**, *92*, 10–24. [[CrossRef](#)] [[PubMed](#)]
137. Zheng, M.; Li, K.; Chen, T.; Liu, S.; He, L. Geniposide protects depression through BTK/JAK2/STAT1 signaling pathway in lipopolysaccharide-induced depressive mice. *Brain Res. Bull.* **2021**, *170*, 65–73. [[CrossRef](#)] [[PubMed](#)]
138. Huggett, S.B.; Hatfield, J.S.; Walters, J.D.; McGeary, J.E.; Welsh, J.W.; Mackay, T.F.C.; Anholt, R.R.H.; Palmer, R.H.C. Ibrutinib as a potential therapeutic for cocaine use disorder. *Transl. Psychiatry* **2021**, *11*, 623. [[CrossRef](#)]
139. Zhan, Y.; Krafft, P.R.; Lekic, T.; Ma, Q.; Souvenir, R.; Zhang, J.H.; Tang, J. Imatinib preserves blood-brain barrier integrity following experimental subarachnoid hemorrhage in rats. *J. Neurosci. Res.* **2015**, *93*, 94–103. [[CrossRef](#)]
140. Shiba, M.; Fujimoto, M.; Kawakita, F.; Imanaka-Yoshida, K.; Yoshida, T.; Kanamaru, K.; Taki, W.; Suzuki, H. Effects of tenascin-C on early brain injury after subarachnoid hemorrhage in rats. *Acta Neurochir. Suppl.* **2015**, *120*, 69–73. [[CrossRef](#)]
141. Changlong, Z.; Guangwei, Z.; Xuenong, H.; Xiaohui, X.; Xiaochuan, S.; Yanfeng, X. The Role of Platelet-Derived Growth Factor Receptor in Early Brain Injury Following Subarachnoid Hemorrhage. *J. Stroke Cerebrovasc. Dis.* **2016**, *25*, 2203–2208. [[CrossRef](#)]
142. Shiba, M.; Fujimoto, M.; Imanaka-Yoshida, K.; Yoshida, T.; Taki, W.; Suzuki, H. Tenascin-C causes neuronal apoptosis after subarachnoid hemorrhage in rats. *Transl. Stroke Res.* **2014**, *5*, 238–247. [[CrossRef](#)]
143. Shiba, M.; Suzuki, H.; Fujimoto, M.; Shimojo, N.; Imanaka-Yoshida, K.; Yoshida, T.; Kanamaru, K.; Matsushima, S.; Taki, W. Imatinib mesylate prevents cerebral vasospasm after subarachnoid hemorrhage via inhibiting tenascin-C expression in rats. *Neurobiol. Dis.* **2012**, *46*, 172–179. [[CrossRef](#)] [[PubMed](#)]
144. Shiba, M.; Suzuki, H.; Fujimoto, M.; Shimojo, N.; Imanaka-Yoshida, K.; Yoshida, T.; Kanamaru, K.; Matsushima, S.; Taki, W. Role of platelet-derived growth factor in cerebral vasospasm after subarachnoid hemorrhage in rats. *Acta Neurochir. Suppl.* **2013**, *115*, 219–223. [[CrossRef](#)] [[PubMed](#)]
145. Ma, Q.; Huang, B.; Khatibi, N.; Rolland, W., 2nd; Suzuki, H.; Zhang, J.H.; Tang, J. PDGFR- $\alpha$  inhibition preserves blood-brain barrier after intracerebral hemorrhage. *Ann. Neurol.* **2011**, *70*, 920–931. [[CrossRef](#)] [[PubMed](#)]
146. Yang, P.; Manaenko, A.; Xu, F.; Miao, L.; Wang, G.; Hu, X.; Guo, Z.N.; Hu, Q.; Hartman, R.E.; Pearce, W.J.; et al. Role of PDGF-D and PDGFR- $\beta$  in neuroinflammation in experimental ICH mice model. *Exp. Neurol.* **2016**, *283*, 157–164. [[CrossRef](#)]
147. Yang, P.; Wu, J.; Miao, L.; Manaenko, A.; Matei, N.; Zhang, Y.; Xu, L.; Pearce, W.J.; Hartman, R.E.; Obenaus, A.; et al. Platelet-Derived Growth Factor Receptor- $\beta$  Regulates Vascular Smooth Muscle Cell Phenotypic Transformation and Neuroinflammation After Intracerebral Hemorrhage in Mice. *Crit. Care Med.* **2016**, *44*, e390–e402. [[CrossRef](#)]
148. Pearce, W.J.; Doan, C.; Carreon, D.; Kim, D.; Durrant, L.M.; Manaenko, A.; McCoy, L.; Obenaus, A.; Zhang, J.H.; Tang, J. Imatinib attenuates cerebrovascular injury and phenotypic transformation after intracerebral hemorrhage in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2016**, *311*, R1093–R1104. [[CrossRef](#)]
149. Sun, Z.; Gao, C.; Gao, D.; Sun, R.; Li, W.; Wang, F.; Wang, Y.; Cao, H.; Zhou, G.; Zhang, J.; et al. Reduction in pericyte coverage leads to blood-brain barrier dysfunction via endothelial transcytosis following chronic cerebral hypoperfusion. *Fluids Barriers CNS* **2021**, *18*, 21. [[CrossRef](#)]
150. Sakai, K.; Takata, F.; Yamanaka, G.; Yasunaga, M.; Hashiguchi, K.; Tominaga, K.; Itoh, K.; Kataoka, Y.; Yamauchi, A.; Dohgu, S. Reactive pericytes in early phase are involved in glial activation and late-onset hypersusceptibility to pilocarpine-induced seizures in traumatic brain injury model mice. *J. Pharmacol. Sci.* **2021**, *145*, 155–165. [[CrossRef](#)]
151. Klement, W.; Blaquiere, M.; Zub, E.; deBock, F.; Boux, F.; Barbier, E.; Audinat, E.; Lerner-Natoli, M.; Marchi, N. A pericyte-glia scarring develops at the leaky capillaries in the hippocampus during seizure activity. *Epilepsia* **2019**, *60*, 1399–1411. [[CrossRef](#)]
152. Su, E.J.; Fredriksson, L.; Kanzawa, M.; Moore, S.; Folestad, E.; Stevenson, T.K.; Nilsson, I.; Sashindranath, M.; Schielke, G.P.; Warnock, M.; et al. Imatinib treatment reduces brain injury in a murine model of traumatic brain injury. *Front. Cell Neurosci.* **2015**, *9*, 385. [[CrossRef](#)]
153. Wang, J.; Bai, T.; Wang, N.; Li, H.; Guo, X. Neuroprotective potential of imatinib in global ischemia-reperfusion-induced cerebral injury: Possible role of Janus-activated kinase 2/signal transducer and activator of transcription 3 and connexin 43. *Korean J. Physiol. Pharmacol.* **2020**, *24*, 11–18. [[CrossRef](#)] [[PubMed](#)]
154. Merali, Z.; Leung, J.; Mikulis, D.; Silver, F.; Kassner, A. Longitudinal assessment of imatinib's effect on the blood-brain barrier after ischemia/reperfusion injury with permeability MRI. *Transl. Stroke Res.* **2015**, *6*, 39–49. [[CrossRef](#)] [[PubMed](#)]
155. Gardner, L.E.; White, J.D.; Eimerbrink, M.J.; Boehm, G.W.; Chumley, M.J. Imatinib methanesulfonate reduces hyperphosphorylation of tau following repeated peripheral exposure to lipopolysaccharide. *Neuroscience* **2016**, *331*, 72–77. [[CrossRef](#)] [[PubMed](#)]
156. Weintraub, M.K.; Bisson, C.M.; Nouri, J.N.; Vinson, B.T.; Eimerbrink, M.J.; Kranjac, D.; Boehm, G.W.; Chumley, M.J. Imatinib methanesulfonate reduces hippocampal amyloid- $\beta$  and restores cognitive function following repeated endotoxin exposure. *Brain Behav. Immun.* **2013**, *33*, 24–28. [[CrossRef](#)] [[PubMed](#)]
157. Sun, W.; Netzer, W.J.; Sinha, A.; Gindinova, K.; Chang, E.; Sinha, S.C. Development of Gleevec Analogues for Reducing Production of  $\beta$ -Amyloid Peptides through Shifting  $\beta$ -Cleavage of Amyloid Precursor Proteins. *J. Med. Chem.* **2019**, *62*, 3122–3134. [[CrossRef](#)]
158. Bauer, C.; Pardossi-Piquard, R.; Dunys, J.; Roy, M.; Checler, F.  $\gamma$ -Secretase-mediated regulation of neprilysin: Influence of cell density and aging and modulation by imatinib. *J. Alzheimer's Dis.* **2011**, *27*, 511–520. [[CrossRef](#)]
159. Sutcliffe, J.G.; Hedlund, P.B.; Thomas, E.A.; Bloom, F.E.; Hilbush, B.S. Peripheral reduction of  $\beta$ -amyloid is sufficient to reduce brain  $\beta$ -amyloid: Implications for Alzheimer's disease. *J. Neurosci. Res.* **2011**, *89*, 808–814. [[CrossRef](#)]

160. Hussain, I.; Fabrègue, J.; Anderes, L.; Ousson, S.; Borlat, F.; Eligert, V.; Berger, S.; Dimitrov, M.; Alattia, J.R.; Fraering, P.C.; et al. The role of  $\gamma$ -secretase activating protein (GSAP) and imatinib in the regulation of  $\gamma$ -secretase activity and amyloid- $\beta$  generation. *J. Biol. Chem.* **2013**, *288*, 2521–2531. [[CrossRef](#)]
161. Netzer, W.J.; Bettayeb, K.; Sinha, S.C.; Flajolet, M.; Greengard, P.; Bustos, V. Gleevec shifts APP processing from a  $\beta$ -cleavage to a nonamyloidogenic cleavage. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 1389–1394. [[CrossRef](#)]
162. Estrada, L.D.; Chamorro, D.; Yáñez, M.J.; Gonzalez, M.; Leal, N.; von Bernhardi, R.; Dulcey, A.E.; Marugan, J.; Ferrer, M.; Soto, C.; et al. Reduction of Blood Amyloid- $\beta$  Oligomers in Alzheimer's Disease Transgenic Mice by c-Abl Kinase Inhibition. *J. Alzheimer's Dis.* **2016**, *54*, 1193–1205. [[CrossRef](#)]
163. Netzer, W.J.; Dou, F.; Cai, D.; Veach, D.; Jean, S.; Li, Y.; Bornmann, W.G.; Clarkson, B.; Xu, H.; Greengard, P. Gleevec inhibits beta-amyloid production but not Notch cleavage. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12444–12449. [[CrossRef](#)] [[PubMed](#)]
164. Chu, J.; Lauretti, E.; Craige, C.P.; Praticò, D. Pharmacological modulation of GSAP reduces amyloid- $\beta$  levels and tau phosphorylation in a mouse model of Alzheimer's disease with plaques and tangles. *J. Alzheimer's Dis.* **2014**, *41*, 729–737. [[CrossRef](#)] [[PubMed](#)]
165. Alvarez, A.R.; Sandoval, P.C.; Leal, N.R.; Castro, P.U.; Kosik, K.S. Activation of the neuronal c-Abl tyrosine kinase by amyloid-beta-peptide and reactive oxygen species. *Neurobiol. Dis.* **2004**, *17*, 326–336. [[CrossRef](#)] [[PubMed](#)]
166. Cancino, G.I.; Toledo, E.M.; Leal, N.R.; Hernandez, D.E.; Yévenes, L.F.; Inestrosa, N.C.; Alvarez, A.R. STI571 prevents apoptosis, tau phosphorylation and behavioural impairments induced by Alzheimer's beta-amyloid deposits. *Brain* **2008**, *131*, 2425–2442. [[CrossRef](#)] [[PubMed](#)]
167. Kerridge, C.; Belyaev, N.D.; Nalivaeva, N.N.; Turner, A.J. The A $\beta$ -clearance protein transthyretin, like neprilysin, is epigenetically regulated by the amyloid precursor protein intracellular domain. *J. Neurochem.* **2014**, *130*, 419–431. [[CrossRef](#)]
168. He, G.; Luo, W.; Li, P.; Remmers, C.; Netzer, W.J.; Hendrick, J.; Bettayeb, K.; Flajolet, M.; Gorelick, F.; Wennogle, L.P.; et al. Gamma-secretase activating protein is a therapeutic target for Alzheimer's disease. *Nature* **2010**, *467*, 95–98. [[CrossRef](#)]
169. Reichenstein, M.; Borovok, N.; Sheinin, A.; Brider, T.; Michaelievski, I. Abelson Kinases Mediate the Depression of Spontaneous Synaptic Activity Induced by Amyloid Beta 1-42 Peptides. *Cell Mol. Neurobiol.* **2021**, *41*, 431–448. [[CrossRef](#)]
170. Peng, Q.; Zhang, M.; Shi, G. High-Performance Extended-Gate Field-Effect Transistor for Kinase Sensing in A $\beta$  Accumulation of Alzheimer's Disease. *Anal. Chem.* **2022**, *94*, 1491–1497. [[CrossRef](#)]
171. Ren, Y.; Chen, J.; Wu, X.; Gui, C.; Mao, K.; Zou, F.; Li, W. Role of c-Abl-GSK3 $\beta$  Signaling in MPP $^{+}$ -Induced Autophagy-Lysosomal Dysfunction. *Toxicol. Sci.* **2018**, *165*, 232–243. [[CrossRef](#)]
172. Wu, R.; Chen, H.; Ma, J.; He, Q.; Huang, Q.; Liu, Q.; Li, M.; Yuan, Z. c-Abl-p38 $\alpha$  signaling plays an important role in MPTP-induced neuronal death. *Cell Death Differ.* **2016**, *23*, 542–552. [[CrossRef](#)]
173. Imam, S.Z.; Zhou, Q.; Yamamoto, A.; Valente, A.J.; Ali, S.F.; Bains, M.; Roberts, J.L.; Kahle, P.J.; Clark, R.A.; Li, S. Novel regulation of parkin function through c-Abl-mediated tyrosine phosphorylation: Implications for Parkinson's disease. *J. Neurosci.* **2011**, *31*, 157–163. [[CrossRef](#)] [[PubMed](#)]
174. Yamamura, Y.; Morigaki, R.; Kasahara, J.; Yokoyama, H.; Tanabe, A.; Okita, S.; Koizumi, H.; Nagahiro, S.; Kaji, R.; Goto, S. Dopamine signaling negatively regulates striatal phosphorylation of Cdk5 at tyrosine 15 in mice. *Front. Cell Neurosci.* **2013**, *7*, 12. [[CrossRef](#)] [[PubMed](#)]
175. Pan, Y.; Sun, L.; Wang, J.; Fu, W.; Fu, Y.; Wang, J.; Tong, Y.; Pan, B. STI571 protects neuronal cells from neurotoxic prion protein fragment-induced apoptosis. *Neuropharmacology* **2015**, *93*, 191–198. [[CrossRef](#)] [[PubMed](#)]
176. Aguib, Y.; Heiseke, A.; Gilch, S.; Riemer, C.; Baier, M.; Schätzl, H.M.; Ertmer, A. Autophagy induction by trehalose counteracts cellular prion infection. *Autophagy* **2009**, *5*, 361–369. [[CrossRef](#)] [[PubMed](#)]
177. Yun, S.W.; Ertmer, A.; Flechsig, E.; Gilch, S.; Riederer, P.; Gerlach, M.; Schätzl, H.M.; Klein, M.A. The tyrosine kinase inhibitor imatinib mesylate delays prion neuroinvasion by inhibiting prion propagation in the periphery. *J. Neurovirol.* **2007**, *13*, 328–337. [[CrossRef](#)] [[PubMed](#)]
178. Ertmer, A.; Gilch, S.; Yun, S.W.; Flechsig, E.; Klebl, B.; Stein-Gerlach, M.; Klein, M.A.; Schätzl, H.M. The tyrosine kinase inhibitor STI571 induces cellular clearance of PrP $^{Sc}$  in prion-infected cells. *J. Biol. Chem.* **2004**, *279*, 41918–41927. [[CrossRef](#)]
179. Rojas, F.; Gonzalez, D.; Cortes, N.; Ampuero, E.; Hernández, D.E.; Fritz, E.; Abarzua, S.; Martinez, A.; Elorza, A.A.; Alvarez, A.; et al. Reactive oxygen species trigger motoneuron death in non-cell-autonomous models of ALS through activation of c-Abl signaling. *Front. Cell Neurosci.* **2015**, *9*, 203. [[CrossRef](#)]
180. Kegel, K.B.; Sapp, E.; Alexander, J.; Reeves, P.; Bleckmann, D.; Sobin, L.; Masso, N.; Valencia, A.; Jeong, H.; Krainc, D.; et al. Huntingtin cleavage product A forms in neurons and is reduced by gamma-secretase inhibitors. *Mol. Neurodegener.* **2010**, *5*, 58. [[CrossRef](#)]
181. Nacer, A.; Movila, A.; Baer, K.; Mikolajczak, S.A.; Kappe, S.H.; Frevert, U. Neuroimmunological blood brain barrier opening in experimental cerebral malaria. *PLoS Pathog* **2012**, *8*, e1002982. [[CrossRef](#)]
182. Vlastic, V.; Simakajornboon, N.; Gozal, E.; Gozal, D. PDGF-beta receptor expression in the dorsocaudal brainstem parallels hypoxic ventilatory depression in the developing rat. *Pediatr. Res.* **2001**, *50*, 236–241. [[CrossRef](#)]
183. Yáñez, M.J.; Belbin, O.; Estrada, L.D.; Leal, N.; Contreras, P.S.; Lleó, A.; Burgos, P.V.; Zanlungo, S.; Alvarez, A.R. c-Abl links APP-BACE1 interaction promoting APP amyloidogenic processing in Niemann-Pick type C disease. *Biochim. Biophys. Acta* **2016**, *1862*, 2158–2167. [[CrossRef](#)] [[PubMed](#)]



184. Marín, T.; Dulcey, A.E.; Campos, F.; de la Fuente, C.; Acuña, M.; Castro, J.; Pinto, C.; Yañez, M.J.; Cortez, C.; McGrath, D.W.; et al. c-Abl Activation Linked to Autophagy-Lysosomal Dysfunction Contributes to Neurological Impairment in Niemann-Pick Type A Disease. *Front. Cell Dev. Biol.* **2022**, *10*, 844297. [[CrossRef](#)] [[PubMed](#)]
185. Yañez, M.J.; Campos, F.; Marín, T.; Klein, A.D.; Futerman, A.H.; Alvarez, A.R.; Zanolungo, S. c-Abl activates RIPK3 signaling in Gaucher disease. *Biochim. Biophys. Acta Mol. Basis Dis.* **2021**, *1867*, 166089. [[CrossRef](#)] [[PubMed](#)]
186. Potula, R.; Dhillon, N.; Sui, Y.; Zien, C.A.; Funai, K.; Pinson, D.; Mayo, M.S.; Singh, D.K.; Narayan, O.; Buch, S. Association of platelet-derived growth factor-B chain with simian human immunodeficiency virus encephalitis. *Am. J. Pathol.* **2004**, *165*, 815–824. [[CrossRef](#)] [[PubMed](#)]
187. Jia, X.; Zhang, A.; Li, Z.; Peng, X.; Tian, X.; Gao, F. Activation of spinal PDGFR $\beta$  in microglia promotes neuronal autophagy via p38 MAPK pathway in morphine-tolerant rats. *J. Neurochem.* **2021**, *158*, 373–390. [[CrossRef](#)]
188. Jia, J.N.; Yin, X.X.; Li, Q.; Guan, Q.W.; Yang, N.; Chen, K.N.; Zhou, H.H.; Mao, X.Y. Neuroprotective Effects of the Anti-cancer Drug Lapatinib Against Epileptic Seizures via Suppressing Glutathione Peroxidase 4-Dependent Ferroptosis. *Front. Pharmacol.* **2020**, *11*, 601572. [[CrossRef](#)]
189. Xu, H.Y.; Sun, Y.J.; Sun, Y.Y.; Wu, Y.J.; Xu, M.Y.; Chen, L.P.; Zhu, L. Lapatinib alleviates TOCP-induced axonal damage in the spinal cord of mouse. *Neuropharmacology* **2021**, *189*, 108535. [[CrossRef](#)]
190. Mansour, H.M.; Fawzy, H.M.; El-Khatib, A.S.; Khattab, M.M. Lapatinib ditosylate rescues memory impairment in D-galactose/ovariectomized rats: Potential repositioning of an anti-cancer drug for the treatment of Alzheimer's disease. *Exp. Neurol.* **2021**, *341*, 113697. [[CrossRef](#)]
191. Mansour, H.M.; Fawzy, H.M.; El-Khatib, A.S.; Khattab, M.M. Inhibition of mitochondrial pyruvate carrier 1 by lapatinib ditosylate mitigates Alzheimer's-like disease in D-galactose/ovariectomized rats. *Neurochem. Int.* **2021**, *150*, 105178. [[CrossRef](#)]
192. Zavvarian, M.M.; Hong, J.; Khazaei, M.; Chio, J.C.T.; Wang, J.; Badner, A.; Fehlings, M.G. The Protein Kinase Inhibitor Midostaurin Improves Functional Neurological Recovery and Attenuates Inflammatory Changes Following Traumatic Cervical Spinal Cord Injury. *Biomolecules* **2021**, *11*, 972. [[CrossRef](#)]
193. Dent, P.; Booth, L.; Roberts, J.L.; Poklepovic, A.; Cridebring, D.; Reiman, E.M. Inhibition of heat shock proteins increases autophagosome formation, and reduces the expression of APP, Tau, SOD1 G93A and TDP-43. *Aging Albany NY* **2021**, *13*, 17097–17117. [[CrossRef](#)] [[PubMed](#)]
194. Attia, G.M.; Elmansy, R.A.; Elsaed, W.M. Neuroprotective effect of nilotinib on pentylentetrazol-induced epilepsy in adult rat hippocampus: Involvement of oxidative stress, autophagy, inflammation, and apoptosis. *Folia Neuropathol.* **2019**, *57*, 146–160. [[CrossRef](#)] [[PubMed](#)]
195. Lonskaya, I.; Hebron, M.; Chen, W.; Schachter, J.; Moussa, C. Tau deletion impairs intracellular  $\beta$ -amyloid-42 clearance and leads to more extracellular plaque deposition in gene transfer models. *Mol. Neurodegener.* **2014**, *9*, 46. [[CrossRef](#)] [[PubMed](#)]
196. Liu, X.; Hebron, M.; Shi, W.; Lonskaya, I.; Moussa, C.E. Ubiquitin specific protease-13 independently regulates parkin ubiquitination and alpha-synuclein clearance in alpha-synucleinopathies. *Hum. Mol. Genet.* **2019**, *28*, 548–560. [[CrossRef](#)] [[PubMed](#)]
197. Mahul-Mellier, A.L.; Fauvet, B.; Gysbers, A.; Dikiy, I.; Oueslati, A.; Georgeon, S.; Lamontanara, A.J.; Bisquertt, A.; Eliezer, D.; Masliah, E.; et al. c-Abl phosphorylates  $\alpha$ -synuclein and regulates its degradation: Implication for  $\alpha$ -synuclein clearance and contribution to the pathogenesis of Parkinson's disease. *Hum. Mol. Genet.* **2014**, *23*, 2858–2879. [[CrossRef](#)]
198. Imberdis, T.; Negri, J.; Ramalingam, N.; Terry-Kantor, E.; Ho, G.P.H.; Fanning, S.; Stirtz, G.; Kim, T.E.; Levy, O.A.; Young-Pearse, T.L.; et al. Cell models of lipid-rich  $\alpha$ -synuclein aggregation validate known modifiers of  $\alpha$ -synuclein biology and identify stearyl-CoA desaturase. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 20760–20769. [[CrossRef](#)]
199. Adlimoghaddam, A.; Odero, G.G.; Glazner, G.; Turner, R.S.; Albensi, B.C. Nilotinib Improves Bioenergetic Profiling in Brain Astroglia in the 3xTg Mouse Model of Alzheimer's Disease. *Aging Dis.* **2021**, *12*, 441–465. [[CrossRef](#)]
200. La Barbera, L.; Vedele, F.; Nobili, A.; Krashia, P.; Spoletti, E.; Latagliata, E.C.; Cutuli, D.; Cauzzi, E.; Marino, R.; Viscomi, M.T.; et al. Nilotinib restores memory function by preventing dopaminergic neuron degeneration in a mouse model of Alzheimer's Disease. *Prog. Neurobiol.* **2021**, *202*, 102031. [[CrossRef](#)]
201. Nobili, A.; La Barbera, L.; D'Amelio, M. Targeting autophagy as a therapeutic strategy to prevent dopamine neuron loss in early stages of Alzheimer disease. *Autophagy* **2021**, *17*, 1278–1280. [[CrossRef](#)]
202. Wu, J.; Xu, X.; Zheng, L.; Mo, J.; Jin, X.; Bao, Y. Nilotinib inhibits microglia-mediated neuroinflammation to protect against dopaminergic neuronal death in Parkinson's disease models. *Int. Immunopharmacol.* **2021**, *99*, 108025. [[CrossRef](#)]
203. Kuo, Y.C.; Tsai, H.C.; Rajesh, R. Glutathione Liposomes Carrying Ceftriaxone, FK506, and Nilotinib to Control Overexpressed Dopamine Markers and Apoptotic Factors in Neurons. *ACS Biomater. Sci. Eng.* **2021**, *7*, 3242–3255. [[CrossRef](#)] [[PubMed](#)]
204. Kim, H.; Shin, J.Y.; Jo, A.; Kim, J.H.; Park, S.; Choi, J.Y.; Kang, H.C.; Dawson, V.L.; Dawson, T.M.; Shin, J.H.; et al. Parkin interacting substrate phosphorylation by c-Abl drives dopaminergic neurodegeneration. *Brain* **2021**, *144*, 3674–3691. [[CrossRef](#)] [[PubMed](#)]
205. Peikert, K.; Federti, E.; Matte, A.; Constantin, G.; Pietronigro, E.C.; Fabene, P.F.; Defilippi, P.; Turco, E.; Del Gallo, F.; Pucci, P.; et al. Therapeutic targeting of Lyn kinase to treat chorea-acanthocytosis. *Acta Neuropathol. Commun.* **2021**, *9*, 81. [[CrossRef](#)] [[PubMed](#)]
206. Federti, E.; Matte, A.; Riccardi, V.; Peikert, K.; Alper, S.L.; Danek, A.; Walker, R.H.; Siciliano, A.; Iatcenko, I.; Hermann, A.; et al. Adaptive Up-Regulation of PRX2 and PRX5 Expression Characterizes Brain from a Mouse Model of Chorea-Acanthocytosis. *Antioxidants* **2021**, *11*, 76. [[CrossRef](#)]

207. Hor, J.H.; Soh, E.S.; Tan, L.Y.; Lim, V.J.W.; Santosa, M.M.; Winanto; Ho, B.X.; Fan, Y.; Soh, B.S.; Ng, S.Y. Cell cycle inhibitors protect motor neurons in an organoid model of Spinal Muscular Atrophy. *Cell Death Dis.* **2018**, *9*, 1100. [[CrossRef](#)]
208. Chao, A.C.; Chen, C.H.; Chang, S.H.; Huang, C.T.; Hwang, W.C.; Yang, D.I. Id1 and Sonic Hedgehog Mediate Cell Cycle Reentry and Apoptosis Induced by Amyloid Beta-Peptide in Post-mitotic Cortical Neurons. *Mol. Neurobiol.* **2019**, *56*, 465–489. [[CrossRef](#)]
209. Esteras, N.; Alquézar, C.; Bartolomé, F.; de la Encarnación, A.; Bermejo-Pareja, F.; Molina, J.A.; Martín-Requero, Á. G1/S Cell Cycle Checkpoint Dysfunction in Lymphoblasts from Sporadic Parkinson's Disease Patients. *Mol. Neurobiol.* **2015**, *52*, 386–398. [[CrossRef](#)]
210. Javidnia, M.; Hebron, M.L.; Xin, Y.; Kinney, N.G.; Moussa, C.E. Pazopanib Reduces Phosphorylated Tau Levels and Alters Astrocytes in a Mouse Model of Tauopathy. *J. Alzheimer's Dis.* **2017**, *60*, 461–481. [[CrossRef](#)]
211. Yang, Y.; Li, G.; Zhao, D.; Yu, H.; Zheng, X.; Peng, X.; Zhang, X.; Fu, T.; Hu, X.; Niu, M.; et al. Computational discovery and experimental verification of tyrosine kinase inhibitor pazopanib for the reversal of memory and cognitive deficits in rat model neurodegeneration. *Chem. Sci.* **2015**, *6*, 2812–2821. [[CrossRef](#)]
212. Li, M.; Li, Z.; Ren, H.; Jin, W.N.; Wood, K.; Liu, Q.; Sheth, K.N.; Shi, F.D. Colony stimulating factor 1 receptor inhibition eliminates microglia and attenuates brain injury after intracerebral hemorrhage. *J. Cereb. Blood Flow Metab.* **2017**, *37*, 2383–2395. [[CrossRef](#)]
213. Shi, E.; Shi, K.; Qiu, S.; Sheth, K.N.; Lawton, M.T.; Ducruet, A.F. Chronic inflammation, cognitive impairment, and distal brain region alteration following intracerebral hemorrhage. *FASEB J.* **2019**, *33*, 9616–9626. [[CrossRef](#)] [[PubMed](#)]
214. Heinz, R.; Brandenburg, S.; Nieminen-Kelhä, M.; Kremenetskaia, I.; Boehm-Sturm, P.; Vajkoczy, P.; Schneider, U.C. Microglia as target for anti-inflammatory approaches to prevent secondary brain injury after subarachnoid hemorrhage (SAH). *J. Neuroinflamm.* **2021**, *18*, 36. [[CrossRef](#)] [[PubMed](#)]
215. Shen, Q.; Zhang, G. Depletion of microglia mitigates cerebrovascular dysfunction in diet-induced obesity mice. *Am. J. Physiol. Endocrinol. Metab.* **2021**, *321*, E367–E375. [[CrossRef](#)] [[PubMed](#)]
216. Rice, R.A.; Spangenberg, E.E.; Yamate-Morgan, H.; Lee, R.J.; Arora, R.P.; Hernandez, M.X.; Tenner, A.J.; West, B.L.; Green, K.N. Elimination of Microglia Improves Functional Outcomes Following Extensive Neuronal Loss in the Hippocampus. *J. Neurosci.* **2015**, *35*, 9977–9989. [[CrossRef](#)] [[PubMed](#)]
217. Shi, Y.; Manis, M.; Long, J.; Wang, K.; Sullivan, P.M.; Remolina Serrano, J.; Hoyle, R.; Holtzman, D.M. Microglia drive APOE-dependent neurodegeneration in a tauopathy mouse model. *J. Exp. Med.* **2019**, *216*, 2546–2561. [[CrossRef](#)] [[PubMed](#)]
218. Sosna, J.; Philipp, S.; Albay, R., 3rd; Reyes-Ruiz, J.M.; Baglietto-Vargas, D.; LaFerla, F.M.; Glabe, C.G. Early long-term administration of the CSF1R inhibitor PLX3397 ablates microglia and reduces accumulation of intraneuronal amyloid, neuritic plaque deposition and pre-fibrillar oligomers in 5XFAD mouse model of Alzheimer's disease. *Mol. Neurodegener.* **2018**, *13*, 11. [[CrossRef](#)] [[PubMed](#)]
219. Son, Y.; Jeong, Y.J.; Shin, N.R.; Oh, S.J.; Nam, K.R.; Choi, H.D.; Choi, J.Y.; Lee, H.J. Inhibition of Colony-Stimulating Factor 1 Receptor by PLX3397 Prevents Amyloid Beta Pathology and Rescues Dopaminergic Signaling in Aging 5xFAD Mice. *Int. J. Mol. Sci.* **2020**, *21*, 5553. [[CrossRef](#)]
220. Crapser, J.D.; Ochaba, J.; Soni, N.; Reidling, J.C.; Thompson, L.M.; Green, K.N. Microglial depletion prevents extracellular matrix changes and striatal volume reduction in a model of Huntington's disease. *Brain* **2020**, *143*, 266–288. [[CrossRef](#)]
221. Tahmasebi, F.; Pasbakhsh, P.; Mortezaee, K.; Madadi, S.; Barati, S.; Kashani, I.R. Effect of the CSF1R inhibitor PLX3397 on remyelination of corpus callosum in a cuprizone-induced demyelination mouse model. *J. Cell Biochem.* **2019**, *120*, 10576–10586. [[CrossRef](#)]
222. Groh, J.; Klein, D.; Berve, K.; West, B.L.; Martini, R. Targeting microglia attenuates neuroinflammation-related neural damage in mice carrying human PLP1 mutations. *Glia* **2019**, *67*, 277–290. [[CrossRef](#)]
223. Tahmasebi, F.; Pasbakhsh, P.; Barati, S.; Madadi, S.; Kashani, I.R. The effect of microglial ablation and mesenchymal stem cell transplantation on a cuprizone-induced demyelination model. *J. Cell Physiol.* **2021**, *236*, 3552–3564. [[CrossRef](#)] [[PubMed](#)]
224. Qu, W.; Johnson, A.; Kim, J.H.; Lukowicz, A.; Svedberg, D.; Cvetanovic, M. Inhibition of colony-stimulating factor 1 receptor early in disease ameliorates motor deficits in SCA1 mice. *J. Neuroinflamm.* **2017**, *14*, 107. [[CrossRef](#)] [[PubMed](#)]
225. Pinto, B.; Morelli, G.; Rastogi, M.; Savardi, A.; Fumagalli, A.; Petretto, A.; Bartolucci, M.; Varea, E.; Catelani, T.; Contestabile, A.; et al. Rescuing Over-activated Microglia Restores Cognitive Performance in Juvenile Animals of the Dp(16) Mouse Model of Down Syndrome. *Neuron* **2020**, *108*, 887–904.e12. [[CrossRef](#)] [[PubMed](#)]
226. Ueta, Y.; Miyata, M. Brainstem local microglia induce whisker map plasticity in the thalamus after peripheral nerve injury. *Cell Rep.* **2021**, *34*, 108823. [[CrossRef](#)]
227. da Silva, M.C.M.; Gomes, G.F.; de Barros Fernandes, H.; da Silva, A.M.; Teixeira, A.L.; Moreira, F.A.; de Miranda, A.S.; de Oliveira, A.C.P. Inhibition of CSF1R, a receptor involved in microglia viability, alters behavioral and molecular changes induced by cocaine. *Sci. Rep.* **2021**, *11*, 15989. [[CrossRef](#)]
228. Zhang, D.; Li, S.; Hou, L.; Jing, L.; Ruan, Z.; Peng, B.; Zhang, X.; Hong, J.S.; Zhao, J.; Wang, Q. Microglial activation contributes to cognitive impairments in rotenone-induced mouse Parkinson's disease model. *J. Neuroinflamm.* **2021**, *18*, 4. [[CrossRef](#)]
229. Tian, J.; Guo, S.; Chen, H.; Peng, J.J.; Jia, M.M.; Li, N.S.; Zhang, X.J.; Yang, J.; Luo, X.J.; Peng, J. Combination of Emricasan with Ponatinib Synergistically Reduces Ischemia/Reperfusion Injury in Rat Brain Through Simultaneous Prevention of Apoptosis and Necroptosis. *Transl. Stroke Res.* **2018**, *9*, 382–392. [[CrossRef](#)]
230. Zhang, Y.; Zhang, M.; Zhu, W.; Pan, X.; Wang, Q.; Gao, X.; Wang, C.; Zhang, X.; Liu, Y.; Li, S.; et al. Role of Elevated Thrombospondin-1 in Kainic Acid-Induced Status Epilepticus. *Neurosci. Bull.* **2020**, *36*, 263–276. [[CrossRef](#)]

231. Choi, J.P.; Wang, R.; Yang, X.; Wang, X.; Wang, L.; Ting, K.K.; Foley, M.; Cogger, V.; Yang, Z.; Liu, F.; et al. Ponatinib (AP24534) inhibits MEKK3-KLF signaling and prevents formation and progression of cerebral cavernous malformations. *Sci. Adv.* **2018**, *4*, eaau0731. [[CrossRef](#)]
232. Han, K.M.; Kang, R.J.; Jeon, H.; Lee, H.J.; Lee, J.S.; Park, H.; Gak Jeon, S.; Suk, K.; Seo, J.; Hoe, H.S. Regorafenib Regulates AD Pathology, Neuroinflammation, and Dendritic Spinogenesis in Cells and a Mouse Model of AD. *Cells* **2020**, *9*, 1655. [[CrossRef](#)]
233. Maher, P.; Conti, B. Deciphering the pathways that protect from IL-13-mediated potentiation of oxidative stress-induced dopaminergic nerve cell death. *Cytokine* **2018**, *103*, 114–120. [[CrossRef](#)] [[PubMed](#)]
234. Hosseini, A.; Gharibi, T.; Mohammadzadeh, A.; Ebrahimi-Kalan, A.; Jadidi-Niaragh, F.; Babaloo, Z.; Shanehbandi, D.; Baghbani, E.; Baradaran, B. Ruxolitinib attenuates experimental autoimmune encephalomyelitis (EAE) development as animal models of multiple sclerosis (MS). *Life Sci.* **2021**, *276*, 119395. [[CrossRef](#)] [[PubMed](#)]
235. Yu, X.; Lv, J.; Wu, J.; Chen, Y.; Chen, F.; Wang, L. The autoimmune encephalitis-related cytokine TSLP in the brain primes neuroinflammation by activating the JAK2-NLRP3 axis. *Clin. Exp. Immunol.* **2022**, *207*, 113–122. [[CrossRef](#)] [[PubMed](#)]
236. Sullivan, K.D.; Lewis, H.C.; Hill, A.A.; Pandey, A.; Jackson, L.P.; Cabral, J.M.; Smith, K.P.; Liggett, L.A.; Gomez, E.B.; Galbraith, M.D.; et al. Trisomy 21 consistently activates the interferon response. *Elife* **2016**, *5*, e16220. [[CrossRef](#)] [[PubMed](#)]
237. Takata, F.; Dohgu, S.; Sakaguchi, S.; Sakai, K.; Yamanaka, G.; Iwao, T.; Matsumoto, J.; Kimura, I.; Sezaki, Y.; Tanaka, Y.; et al. Oncostatin-M-Reactive Pericytes Aggravate Blood-Brain Barrier Dysfunction by Activating JAK/STAT3 Signaling In Vitro. *Neuroscience* **2019**, *422*, 12–20. [[CrossRef](#)]
238. Haile, W.B.; Gavegnano, C.; Tao, S.; Jiang, Y.; Schinazi, R.F.; Tyor, W.R. The Janus kinase inhibitor ruxolitinib reduces HIV replication in human macrophages and ameliorates HIV encephalitis in a murine model. *Neurobiol. Dis.* **2016**, *92*, 137–143. [[CrossRef](#)]
239. Zhang, J.; He, H.; Qiao, Y.; Zhou, T.; He, H.; Yi, S.; Zhang, L.; Mo, L.; Li, Y.; Jiang, W.; et al. Priming of microglia with IFN- $\gamma$  impairs adult hippocampal neurogenesis and leads to depression-like behaviors and cognitive defects. *Glia* **2020**, *68*, 2674–2692. [[CrossRef](#)]
240. Chen, X.; Gao, C.; Yan, Y.; Cheng, Z.; Chen, G.; Rui, T.; Luo, C.; Gao, Y.; Wang, T.; Chen, X.; et al. Ruxolitinib exerts neuroprotection via repressing ferroptosis in a mouse model of traumatic brain injury. *Exp. Neurol.* **2021**, *342*, 113762. [[CrossRef](#)]
241. Zhu, H.; Jian, Z.; Zhong, Y.; Ye, Y.; Zhang, Y.; Hu, X.; Pu, B.; Gu, L.; Xiong, X. Janus Kinase Inhibition Ameliorates Ischemic Stroke Injury and Neuroinflammation Through Reducing NLRP3 Inflammasome Activation via JAK2/STAT3 Pathway Inhibition. *Front. Immunol.* **2021**, *12*, 714943. [[CrossRef](#)]
242. Qian, Z.Y.; Kong, R.Y.; Zhang, S.; Wang, B.Y.; Chang, J.; Cao, J.; Wu, C.Q.; Huang, Z.Y.; Duan, A.; Li, H.J.; et al. Ruxolitinib attenuates secondary injury after traumatic spinal cord injury. *Neural Regen. Res.* **2022**, *17*, 2029–2035. [[CrossRef](#)]
243. Alquezar, C.; Esteras, N.; de la Encarnación, A.; Moreno, F.; López de Munain, A.; Martín-Requero, Á. Increasing progranulin levels and blockade of the ERK1/2 pathway: Upstream and downstream strategies for the treatment of progranulin deficient frontotemporal dementia. *Eur Neuropsychopharmacol.* **2015**, *25*, 386–403. [[CrossRef](#)] [[PubMed](#)]
244. Ullrich, M.; Weber, M.; Post, A.M.; Popp, S.; Grein, J.; Zechner, M.; Guerrero González, H.; Kreis, A.; Schmitt, A.G.; Üçeyler, N.; et al. OCD-like behavior is caused by dysfunction of thalamo-amygdala circuits and upregulated TrkB/ERK-MAPK signaling as a result of SPRED2 deficiency. *Mol. Psychiatry* **2018**, *23*, 444–458. [[CrossRef](#)] [[PubMed](#)]
245. Huang, H.J.; Wang, H.T.; Yeh, T.Y.; Lin, B.W.; Shiao, Y.J.; Lo, Y.L.; Lin, A.M. Neuroprotective effect of selumetinib on acrolein-induced neurotoxicity. *Sci. Rep.* **2021**, *11*, 12497. [[CrossRef](#)] [[PubMed](#)]
246. Fei, X.; Dou, Y.N.; Wang, L.; Wu, X.; Huan, Y.; Wu, S.; He, X.; Lv, W.; Wei, J.; Fei, Z. Homer1 promotes the conversion of A1 astrocytes to A2 astrocytes and improves the recovery of transgenic mice after intracerebral hemorrhage. *J. Neuroinflamm.* **2022**, *19*, 67. [[CrossRef](#)] [[PubMed](#)]
247. Talebi, A.; Rahnema, M.; Bigdeli, M.R. Effect of intravenous injection of antagomiR-1 on brain ischemia. *Mol. Biol. Rep.* **2019**, *46*, 1149–1155. [[CrossRef](#)] [[PubMed](#)]
248. Guo, W.; Feng, G.; Miao, Y.; Liu, G.; Xu, C. Rapamycin alleviates brain edema after focal cerebral ischemia reperfusion in rats. *Immunopharmacol. Immunotoxicol.* **2014**, *36*, 211–223. [[CrossRef](#)]
249. Wang, J.; Lin, X.; Mu, Z.; Shen, F.; Zhang, L.; Xie, Q.; Tang, Y.; Wang, Y.; Zhang, Z.; Yang, G.Y. Rapamycin Increases Collateral Circulation in Rodent Brain after Focal Ischemia as detected by Multiple Modality Dynamic Imaging. *Theranostics* **2019**, *9*, 4923–4934. [[CrossRef](#)]
250. Chauhan, A.; Sharma, U.; Jagannathan, N.R.; Gupta, Y.K. Rapamycin ameliorates brain metabolites alterations after transient focal ischemia in rats. *Eur. J. Pharmacol.* **2015**, *757*, 28–33. [[CrossRef](#)]
251. Chi, O.Z.; Kiss, G.K.; Mellender, S.J.; Liu, X.; Weiss, H.R. Rapamycin decreased blood-brain barrier permeability in control but not in diabetic rats in early cerebral ischemia. *Neurosci. Lett.* **2017**, *654*, 17–22. [[CrossRef](#)]
252. Liu, P.; Yang, X.; Hei, C.; Meli, Y.; Niu, J.; Sun, T.; Li, P.A. Rapamycin Reduced Ischemic Brain Damage in Diabetic Animals Is Associated with Suppressions of mTOR and ERK1/2 Signaling. *Int. J. Biol. Sci.* **2016**, *12*, 1032–1040. [[CrossRef](#)]
253. Liang, G.; Niu, Y.; Li, Y.; Wei, A.; Dong, J.; Zeng, L. Rapamycin treatment starting at 24 h after cerebral ischemia/reperfusion exhibits protective effect on brain injury in rats. *Zhejiang Da Xue Xue Bao Yi Xue Ban* **2018**, *47*, 443–449. [[PubMed](#)]
254. Yang, X.; Hei, C.; Liu, P.; Song, Y.; Thomas, T.; Tshimanga, S.; Wang, F.; Niu, J.; Sun, T.; Li, P.A. Inhibition of mTOR Pathway by Rapamycin Reduces Brain Damage in Rats Subjected to Transient Forebrain Ischemia. *Int. J. Biol. Sci.* **2015**, *11*, 1424–1435. [[CrossRef](#)] [[PubMed](#)]



255. Park, J.H.; Ahn, J.H.; Song, M.; Kim, H.; Park, C.W.; Park, Y.E.; Lee, T.K.; Lee, J.C.; Kim, D.W.; Lee, C.H.; et al. A 2-Min Transient Ischemia Confers Cerebral Ischemic Tolerance in Non-Obese Gerbils, but Results in Neuronal Death in Obese Gerbils by Increasing Abnormal mTOR Activation-Mediated Oxidative Stress and Neuroinflammation. *Cells* **2019**, *8*, 1126. [[CrossRef](#)] [[PubMed](#)]
256. Mehta, R.I.; Tsymbalyuk, N.; Ivanova, S.; Stokum, J.A.; Woo, K.; Gerzanich, V.; Simard, J.M.  $\alpha$ -Endosulfine (ARPP-19e) Expression in a Rat Model of Stroke. *J. Neuropathol. Exp. Neurol.* **2017**, *76*, 898–907. [[CrossRef](#)] [[PubMed](#)]
257. Carloni, S.; Buonocore, G.; Balduini, W. Protective role of autophagy in neonatal hypoxia-ischemia induced brain injury. *Neurobiol. Dis.* **2008**, *32*, 329–339. [[CrossRef](#)] [[PubMed](#)]
258. Hei, C.; Liu, P.; Yang, X.; Niu, J.; Li, P.A. Inhibition of mTOR signaling Confers Protection against Cerebral Ischemic Injury in Acute Hyperglycemic Rats. *Int. J. Biol. Sci.* **2017**, *13*, 878–887. [[CrossRef](#)]
259. Zhang, B.; Wu, M.; Liu, L.; Zhu, Y.; Kai, J.; Zeng, L. [Inhibiting mammalian target of rapamycin signaling pathway improves cognitive function in mice with chronic cerebral ischemia]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* **2017**, *46*, 405–412. [[PubMed](#)]
260. Li, Q.; Zhang, T.; Wang, J.; Zhang, Z.; Zhai, Y.; Yang, G.Y.; Sun, X. Rapamycin attenuates mitochondrial dysfunction via activation of mitophagy in experimental ischemic stroke. *Biochem. Biophys. Res. Commun.* **2014**, *444*, 182–188. [[CrossRef](#)]
261. Ghiglieri, V.; Pendolino, V.; Bageetta, V.; Sgobio, C.; Calabresi, P.; Picconi, B. mTOR inhibitor rapamycin suppresses striatal post-ischemic LTP. *Exp. Neurol.* **2010**, *226*, 328–331. [[CrossRef](#)]
262. Fletcher, L.; Evans, T.M.; Watts, L.T.; Jimenez, D.F.; Digicaylioglu, M. Rapamycin treatment improves neuron viability in an in vitro model of stroke. *PLoS ONE* **2013**, *8*, e68281. [[CrossRef](#)]
263. Xia, D.Y.; Li, W.; Qian, H.R.; Yao, S.; Liu, J.G.; Qi, X.K. Ischemia preconditioning is neuroprotective in a rat cerebral ischemic injury model through autophagy activation and apoptosis inhibition. *Braz. J. Med. Biol. Res.* **2013**, *46*, 580–588. [[CrossRef](#)] [[PubMed](#)]
264. Su, J.; Zhang, T.; Wang, K.; Zhu, T.; Li, X. Autophagy activation contributes to the neuroprotection of remote ischemic preconditioning against focal cerebral ischemia in rats. *Neurochem. Res.* **2014**, *39*, 2068–2077. [[CrossRef](#)] [[PubMed](#)]
265. Sheng, R.; Zhang, L.S.; Han, R.; Liu, X.Q.; Gao, B.; Qin, Z.H. Autophagy activation is associated with neuroprotection in a rat model of focal cerebral ischemic preconditioning. *Autophagy* **2010**, *6*, 482–494. [[CrossRef](#)] [[PubMed](#)]
266. Yin, L.; Ye, S.; Chen, Z.; Zeng, Y. Rapamycin preconditioning attenuates transient focal cerebral ischemia/reperfusion injury in mice. *Int. J. Neurosci.* **2012**, *122*, 748–756. [[CrossRef](#)] [[PubMed](#)]
267. Sheng, R.; Liu, X.Q.; Zhang, L.S.; Gao, B.; Han, R.; Wu, Y.Q.; Zhang, X.Y.; Qin, Z.H. Autophagy regulates endoplasmic reticulum stress in ischemic preconditioning. *Autophagy* **2012**, *8*, 310–325. [[CrossRef](#)] [[PubMed](#)]
268. Fan, T.; Huang, Z.; Chen, L.; Wang, W.; Zhang, B.; Xu, Y.; Pan, S.; Mao, Z.; Hu, H.; Geng, Q. Associations between autophagy, the ubiquitin-proteasome system and endoplasmic reticulum stress in hypoxia-deoxygenation or ischemia-reperfusion. *Eur. J. Pharmacol.* **2016**, *791*, 157–167. [[CrossRef](#)]
269. Carloni, S.; Girelli, S.; Scopa, C.; Buonocore, G.; Longini, M.; Balduini, W. Activation of autophagy and Akt/CREB signaling play an equivalent role in the neuroprotective effect of rapamycin in neonatal hypoxia-ischemia. *Autophagy* **2010**, *6*, 366–377. [[CrossRef](#)]
270. Hwang, J.Y.; Gertner, M.; Pontarelli, F.; Court-Vazquez, B.; Bennett, M.V.; Ofengeim, D.; Zukin, R.S. Global ischemia induces lysosomal-mediated degradation of mTOR and activation of autophagy in hippocampal neurons destined to die. *Cell Death Differ.* **2017**, *24*, 317–329. [[CrossRef](#)]
271. Xie, L.; Sun, F.; Wang, J.; Mao, X.; Xie, L.; Yang, S.H.; Su, D.M.; Simpkins, J.W.; Greenberg, D.A.; Jin, K. mTOR signaling inhibition modulates macrophage/microglia-mediated neuroinflammation and secondary injury via regulatory T cells after focal ischemia. *J. Immunol.* **2014**, *192*, 6009–6019. [[CrossRef](#)]
272. Lu, Y.; Li, C.; Chen, Q.; Liu, P.; Guo, Q.; Zhang, Y.; Chen, X.; Zhang, Y.; Zhou, W.; Liang, D.; et al. Microthrombus-Targeting Micelles for Neurovascular Remodeling and Enhanced Microcirculatory Perfusion in Acute Ischemic Stroke. *Adv. Mater.* **2019**, *31*, e1808361. [[CrossRef](#)]
273. Qi, H.; Su, F.Y.; Wan, S.; Chen, Y.; Cheng, Y.Q.; Liu, A.J. The antiaging activity and cerebral protection of rapamycin at micro-doses. *CNS Neurosci. Ther.* **2014**, *20*, 991–998. [[CrossRef](#)] [[PubMed](#)]
274. Chauhan, A.; Sharma, U.; Jagannathan, N.R.; Reeta, K.H.; Gupta, Y.K. Rapamycin protects against middle cerebral artery occlusion induced focal cerebral ischemia in rats. *Behav Brain Res.* **2011**, *225*, 603–609. [[CrossRef](#)] [[PubMed](#)]
275. Beard, D.J.; Li, Z.; Schneider, A.M.; Couch, Y.; Cipolla, M.J.; Buchan, A.M. Rapamycin Induces an eNOS (Endothelial Nitric Oxide Synthase) Dependent Increase in Brain Collateral Perfusion in Wistar and Spontaneously Hypertensive Rats. *Stroke* **2020**, *51*, 2834–2843. [[CrossRef](#)] [[PubMed](#)]
276. Wang, C.Y.; Kim, H.H.; Hiroi, Y.; Sawada, N.; Salomone, S.; Benjamin, L.E.; Walsh, K.; Moskowitz, M.A.; Liao, J.K. Obesity increases vascular senescence and susceptibility to ischemic injury through chronic activation of Akt and mTOR. *Sci. Signal.* **2009**, *2*, ra11. [[CrossRef](#)] [[PubMed](#)]
277. Moradpour, S.; Aliaghaei, A.; Bigdeli, M. Effect of Sertoli Cell Transplant and Rapamycin Pretreatment on Middle Cerebral Artery Occlusion-Induced Brain Ischemia in a Rat Model. *Exp. Clin. Transpl.* **2021**, *19*, 1204–1211. [[CrossRef](#)] [[PubMed](#)]
278. Wang, Y.; Wang, Y.; Li, S.; Cui, Y.; Liang, X.; Shan, J.; Gu, W.; Qiu, J.; Li, Y.; Wang, G. Functionalized nanoparticles with monocyte membranes and rapamycin achieve synergistic chemoimmunotherapy for reperfusion-induced injury in ischemic stroke. *J. Nanobiotechnol.* **2021**, *19*, 331. [[CrossRef](#)]

279. Nikolaeva, I.; Crowell, B.; Valenziano, J.; Meaney, D.; D’Arcangelo, G. Beneficial Effects of Early mTORC1 Inhibition after Traumatic Brain Injury. *J. Neurotrauma* **2016**, *33*, 183–193. [[CrossRef](#)]
280. Song, Q.; Xie, D.; Pan, S.; Xu, W. Rapamycin protects neurons from brain contusion-induced inflammatory reaction via modulation of microglial activation. *Mol. Med. Rep.* **2015**, *12*, 7203–7210. [[CrossRef](#)]
281. Fan, Y.Y.; Nan, F.; Guo, B.L.; Liao, Y.; Zhang, M.S.; Guo, J.; Niu, B.L.; Liang, Y.Q.; Yang, C.H.; Zhang, Y.; et al. Effects of long-term rapamycin treatment on glial scar formation after cryogenic traumatic brain injury in mice. *Neurosci. Lett.* **2018**, *678*, 68–75. [[CrossRef](#)]
282. Chen, Y.; Meng, J.; Xu, Q.; Long, T.; Bi, F.; Chang, C.; Liu, W. Rapamycin improves the neuroprotection effect of inhibition of NLRP3 inflammasome activation after TBI. *Brain Res.* **2019**, *1710*, 163–172. [[CrossRef](#)]
283. Wang, C.; Hu, Z.; Zou, Y.; Xiang, M.; Jiang, Y.; Botchway, B.O.A.; Huo, X.; Du, X.; Fang, M. The post-therapeutic effect of rapamycin in mild traumatic brain-injured rats ensuing in the upregulation of autophagy and mitophagy. *Cell Biol. Int.* **2017**, *41*, 1039–1047. [[CrossRef](#)] [[PubMed](#)]
284. Erlich, S.; Alexandrovich, A.; Shohami, E.; Pinkas-Kramarski, R. Rapamycin is a neuroprotective treatment for traumatic brain injury. *Neurobiol. Dis.* **2007**, *26*, 86–93. [[CrossRef](#)] [[PubMed](#)]
285. Ding, K.; Wang, H.; Wu, Y.; Zhang, L.; Xu, J.; Li, T.; Ding, Y.; Zhu, L.; He, J. Rapamycin protects against apoptotic neuronal death and improves neurologic function after traumatic brain injury in mice via modulation of the mTOR-p53-Bax axis. *J. Surg. Res.* **2015**, *194*, 239–247. [[CrossRef](#)] [[PubMed](#)]
286. Campolo, M.; Casili, G.; Lanza, M.; Filippone, A.; Cordaro, M.; Ardizzone, A.; Scuderi, S.A.; Cuzzocrea, S.; Esposito, E.; Paterniti, I. The inhibition of mammalian target of rapamycin (mTOR) in improving inflammatory response after traumatic brain injury. *J. Cell Mol. Med.* **2021**, *25*, 7855–7866. [[CrossRef](#)] [[PubMed](#)]
287. Sasaki, K.; Yamamoto, S.; Mutoh, T.; Tsuru, Y.; Taki, Y.; Kawashima, R. Rapamycin protects against early brain injury independent of cerebral blood flow changes in a mouse model of subarachnoid haemorrhage. *Clin. Exp. Pharmacol. Physiol.* **2018**, *45*, 859–862. [[CrossRef](#)]
288. Zhao, H.; Ji, Z.; Tang, D.; Yan, C.; Zhao, W.; Gao, C. Role of autophagy in early brain injury after subarachnoid hemorrhage in rats. *Mol. Biol. Rep.* **2013**, *40*, 819–827. [[CrossRef](#)]
289. You, W.; Wang, Z.; Li, H.; Shen, H.; Xu, X.; Jia, G.; Chen, G. Inhibition of mammalian target of rapamycin attenuates early brain injury through modulating microglial polarization after experimental subarachnoid hemorrhage in rats. *J. Neurol. Sci.* **2016**, *367*, 224–231. [[CrossRef](#)]
290. Li, J.; Lu, J.; Mi, Y.; Shi, Z.; Chen, C.; Riley, J.; Zhou, C. Voltage-dependent anion channels (VDACs) promote mitophagy to protect neuron from death in an early brain injury following a subarachnoid hemorrhage in rats. *Brain Res.* **2014**, *1573*, 74–83. [[CrossRef](#)]
291. Yamamoto, S.; Mutoh, T.; Sasaki, K.; Mutoh, T.; Taki, Y. Central action of rapamycin on early ischemic injury and related cardiac depression following experimental subarachnoid hemorrhage. *Brain Res. Bull.* **2019**, *144*, 85–91. [[CrossRef](#)]
292. Jing, C.H.; Wang, L.; Liu, P.P.; Wu, C.; Ruan, D.; Chen, G. Autophagy activation is associated with neuroprotection against apoptosis via a mitochondrial pathway in a rat model of subarachnoid hemorrhage. *Neuroscience* **2012**, *213*, 144–153. [[CrossRef](#)]
293. Zhang, W.; Khatibi, N.H.; Yamaguchi-Okada, M.; Yan, J.; Chen, C.; Hu, Q.; Meng, H.; Han, H.; Liu, S.; Zhou, C. Mammalian target of rapamycin (mTOR) inhibition reduces cerebral vasospasm following a subarachnoid hemorrhage injury in canines. *Exp. Neurol.* **2012**, *233*, 799–806. [[CrossRef](#)] [[PubMed](#)]
294. Zhang, X.; Qin, C.; Jing, Y.; Yang, D.; Liu, C.; Gao, F.; Zhang, C.; Talifu, Z.; Yang, M.; Du, L.; et al. Therapeutic effects of rapamycin and surgical decompression in a rabbit spinal cord injury model. *Cell Death Dis.* **2020**, *11*, 567. [[CrossRef](#)]
295. Liu, D.; Jia, S.; Sun, D.; Wang, S.Y.; Meng, F.C.; Guo, W.C. Rapamycin repairs damaged nerve cells and neurological function in rats with spinal cord injury through ERK signaling pathway. *J. Biol. Regul. Homeost. Agents* **2020**, *34*, 865–873. [[CrossRef](#)] [[PubMed](#)]
296. Wang, Z.Y.; Lin, J.H.; Muharram, A.; Liu, W.G. Beclin-1-mediated autophagy protects spinal cord neurons against mechanical injury-induced apoptosis. *Apoptosis* **2014**, *19*, 933–945. [[CrossRef](#)] [[PubMed](#)]
297. Song, Y.; Xue, H.; Liu, T.T.; Liu, J.M.; Chen, D. Rapamycin plays a neuroprotective effect after spinal cord injury via anti-inflammatory effects. *J. Biochem. Mol. Toxicol.* **2015**, *29*, 29–34. [[CrossRef](#)] [[PubMed](#)]
298. Tang, P.; Hou, H.; Zhang, L.; Lan, X.; Mao, Z.; Liu, D.; He, C.; Du, H.; Zhang, L. Autophagy reduces neuronal damage and promotes locomotor recovery via inhibition of apoptosis after spinal cord injury in rats. *Mol. Neurobiol.* **2014**, *49*, 276–287. [[CrossRef](#)] [[PubMed](#)]
299. Goldshmit, Y.; Kanner, S.; Zacs, M.; Frisca, F.; Pinto, A.R.; Currie, P.D.; Pinkas-Kramarski, R. Rapamycin increases neuronal survival, reduces inflammation and astrocyte proliferation after spinal cord injury. *Mol. Cell Neurosci.* **2015**, *68*, 82–91. [[CrossRef](#)]
300. Cordaro, M.; Paterniti, I.; Siracusa, R.; Impellizzeri, D.; Esposito, E.; Cuzzocrea, S. KU0063794, a Dual mTORC1 and mTORC2 Inhibitor, Reduces Neural Tissue Damage and Locomotor Impairment After Spinal Cord Injury in Mice. *Mol. Neurobiol.* **2017**, *54*, 2415–2427. [[CrossRef](#)]
301. Chen, H.C.; Fong, T.H.; Hsu, P.W.; Chiu, W.T. Multifaceted effects of rapamycin on functional recovery after spinal cord injury in rats through autophagy promotion, anti-inflammation, and neuroprotection. *J. Surg. Res.* **2013**, *179*, e203–e210. [[CrossRef](#)]
302. Sekiguchi, A.; Kanno, H.; Ozawa, H.; Yamaya, S.; Itoi, E. Rapamycin promotes autophagy and reduces neural tissue damage and locomotor impairment after spinal cord injury in mice. *J. Neurotrauma* **2012**, *29*, 946–956. [[CrossRef](#)]



303. Hakim, J.S.; Rodysill, B.R.; Chen, B.K.; Schmeichel, A.M.; Yaszemski, M.J.; Windebank, A.J.; Madigan, N.N. Combinatorial tissue engineering partially restores function after spinal cord injury. *J. Tissue Eng. Regen. Med.* **2019**, *13*, 857–873. [[CrossRef](#)] [[PubMed](#)]
304. Lekic, T.; Krafft, P.R.; Klebe, D.; Flores, J.; Rolland, W.B.; Tang, J.; Zhang, J.H. PAR-1, -4, and the mTOR Pathway Following Germinal Matrix Hemorrhage. *Acta Neurochir. Suppl.* **2016**, *121*, 213–216. [[CrossRef](#)] [[PubMed](#)]
305. Lekic, T.; Klebe, D.; McBride, D.W.; Manaenko, A.; Rolland, W.B.; Flores, J.J.; Altay, O.; Tang, J.; Zhang, J.H. Protease-activated receptor 1 and 4 signal inhibition reduces preterm neonatal hemorrhagic brain injury. *Stroke* **2015**, *46*, 1710–1713. [[CrossRef](#)] [[PubMed](#)]
306. Wang, J.P.; Zhang, M.Y. Role for Target of Rapamycin (mTOR) Signal Pathway in Regulating Neuronal Injury after Intracerebral Hemorrhage. *Cell Physiol. Biochem.* **2017**, *41*, 145–153. [[CrossRef](#)] [[PubMed](#)]
307. Lu, Q.; Gao, L.; Huang, L.; Ruan, L.; Yang, J.; Huang, W.; Li, Z.; Zhang, Y.; Jin, K.; Zhuge, Q. Inhibition of mammalian target of rapamycin improves neurobehavioral deficit and modulates immune response after intracerebral hemorrhage in rat. *J. Neuroinflamm.* **2014**, *11*, 44. [[CrossRef](#)] [[PubMed](#)]
308. Li, D.; Liu, F.; Yang, T.; Jin, T.; Zhang, H.; Luo, X.; Wang, M. Rapamycin protects against neuronal death and improves neurological function with modulation of microglia after experimental intracerebral hemorrhage in rats. *Cell. Mol. Biol.* **2016**, *62*, 67–75. [[PubMed](#)]
309. Brewster, A.L.; Lugo, J.N.; Patil, V.V.; Lee, W.L.; Qian, Y.; Vanegas, F.; Anderson, A.E. Rapamycin reverses status epilepticus-induced memory deficits and dendritic damage. *PLoS ONE* **2013**, *8*, e57808. [[CrossRef](#)]
310. Zhang, H.; Xie, Y.; Weng, L.; Zhang, Y.; Shi, Q.; Chen, T.; Zeng, L. Rapamycin improves learning and memory ability in ICR mice with pilocarpine-induced temporal lobe epilepsy. *Zhejiang Da Xue Xue Bao Yi Xue Ban* **2013**, *42*, 602–608.
311. Raffo, E.; Coppola, A.; Ono, T.; Briggs, S.W.; Galanopoulou, A.S. A pulse rapamycin therapy for infantile spasms and associated cognitive decline. *Neurobiol. Dis.* **2011**, *43*, 322–329. [[CrossRef](#)]
312. Aghaie, F.; Shemshaki, A.; Rajabi, M.; Khatami, P.; Hosseini, A. Rapamycin alleviates memory deficit against pentylenetetrazole-induced neural toxicity in Wistar male rats. *Mol. Biol. Rep.* **2021**, *48*, 5083–5091. [[CrossRef](#)]
313. Bornstein, R.; James, K.; Stokes, J.; Park, K.Y.; Kayser, E.B.; Snell, J.; Bard, A.; Chen, Y.; Kalume, F.; Johnson, S.C. Differential effects of mTOR inhibition and dietary ketosis in a mouse model of subacute necrotizing encephalomyelopathy. *Neurobiol. Dis.* **2022**, *163*, 105594. [[CrossRef](#)] [[PubMed](#)]
314. Codeluppi, S.; Svensson, C.I.; Hefferan, M.P.; Valencia, F.; Silldorff, M.D.; Oshiro, M.; Marsala, M.; Pasquale, E.B. The Rheb-mTOR pathway is upregulated in reactive astrocytes of the injured spinal cord. *J. Neurosci.* **2009**, *29*, 1093–1104. [[CrossRef](#)] [[PubMed](#)]
315. Fang, B.; Li, X.Q.; Bao, N.R.; Tan, W.F.; Chen, F.S.; Pi, X.L.; Zhang, Y.; Ma, H. Role of autophagy in the bimodal stage after spinal cord ischemia reperfusion injury in rats. *Neuroscience* **2016**, *328*, 107–116. [[CrossRef](#)] [[PubMed](#)]
316. Chang, K.T.; Lin, Y.L.; Lin, C.T.; Hong, C.J.; Cheng, Y.H.; Tsai, M.J.; Huang, W.C.; Shih, Y.H.; Lee, Y.Y.; Cheng, H.; et al. Neuroprotection in the Acute Stage Enables Functional Recovery Following Repair of Chronic Cervical Root Transection After a 3-Week Delay. *Neurosurgery* **2020**, *87*, 823–832. [[CrossRef](#)]
317. Oku, H.; Morishita, S.; Horie, T.; Kida, T.; Mimura, M.; Kojima, S.; Ikeda, T. P7C3 Suppresses Neuroinflammation and Protects Retinal Ganglion Cells of Rats from Optic Nerve Crush. *Invest. Ophthalmol. Vis. Sci.* **2017**, *58*, 4877–4888. [[CrossRef](#)]
318. Inada, T.; Sato, H.; Hayashi, Y.; Hitomi, S.; Furukawa, A.; Ando, M.; Oshima, E.; Otsuji, J.; Taguchi, N.; Shibuta, I.; et al. Rapamycin Accelerates Axon Regeneration Through Schwann Cell-mediated Autophagy Following Inferior Alveolar Nerve Transection in Rats. *Neuroscience* **2021**, *468*, 43–52. [[CrossRef](#)]
319. Li, N.; Wang, F.; Zhang, Q.; Jin, M.; Lu, Y.; Chen, S.; Guo, C.; Zhang, X. Rapamycin mediates mTOR signaling in reactive astrocytes and reduces retinal ganglion cell loss. *Exp. Eye Res.* **2018**, *176*, 10–19. [[CrossRef](#)]
320. Xu, L.; Zhang, C.; Jiang, N.; He, D.; Bai, Y.; Xin, Y. Rapamycin combined with MCC950 to treat multiple sclerosis in experimental autoimmune encephalomyelitis. *J. Cell Biochem.* **2019**, *120*, 5160–5168. [[CrossRef](#)]
321. Lisi, L.; Navarra, P.; Ciocchi, R.; Sharp, A.; Stigliano, E.; Feinstein, D.L.; Dello Russo, C. Rapamycin reduces clinical signs and neuropathic pain in a chronic model of experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* **2012**, *243*, 43–51. [[CrossRef](#)]
322. Feng, X.; Hou, H.; Zou, Y.; Guo, L. Defective autophagy is associated with neuronal injury in a mouse model of multiple sclerosis. *Bosn. J. Basic Med. Sci.* **2017**, *17*, 95–103. [[CrossRef](#)]
323. Hou, H.; Cao, R.; Quan, M.; Sun, Y.; Sun, H.; Zhang, J.; Li, B.; Guo, L.; Song, X. Rapamycin and fingolimod modulate Treg/Th17 cells in experimental autoimmune encephalomyelitis by regulating the Akt-mTOR and MAPK/ERK pathways. *J. Neuroimmunol.* **2018**, *324*, 26–34. [[CrossRef](#)] [[PubMed](#)]
324. Li, Z.; Nie, L.; Chen, L.; Sun, Y.; Guo, L. Rapamycin alleviates inflammation by up-regulating TGF- $\beta$ /Smad signaling in a mouse model of autoimmune encephalomyelitis. *Nan Fang Yi Ke Da Xue Xue Bao* **2019**, *39*, 35–42. [[CrossRef](#)] [[PubMed](#)]
325. Li, Z.; Nie, L.; Chen, L.; Sun, Y.; Li, G. Rapamycin relieves inflammation of experimental autoimmune encephalomyelitis by altering the balance of Treg/Th17 in a mouse model. *Neurosci. Lett.* **2019**, *705*, 39–45. [[CrossRef](#)] [[PubMed](#)]
326. Hou, H.; Miao, J.; Cao, R.; Han, M.; Sun, Y.; Liu, X.; Guo, L. Rapamycin Ameliorates Experimental Autoimmune Encephalomyelitis by Suppressing the mTOR-STAT3 Pathway. *Neurochem. Res.* **2017**, *42*, 2831–2840. [[CrossRef](#)]
327. Li, Z.; Chen, L.; Niu, X.; Liu, J.; Ping, M.; Li, R.; Xie, X.; Guo, L. Immunomodulatory synergy by combining atorvastatin and rapamycin in the treatment of experimental autoimmune encephalomyelitis (EAE). *J. Neuroimmunol.* **2012**, *250*, 9–17. [[CrossRef](#)]

328. Esposito, M.; Ruffini, F.; Bellone, M.; Gagliani, N.; Battaglia, M.; Martino, G.; Furlan, R. Rapamycin inhibits relapsing experimental autoimmune encephalomyelitis by both effector and regulatory T cells modulation. *J. Neuroimmunol.* **2010**, *220*, 52–63. [[CrossRef](#)]
329. Togha, M.; Jahanshahi, M.; Alizadeh, L.; Jahromi, S.R.; Vakilizadeh, G.; Alipour, B.; Gorji, A.; Ghaemi, A. Rapamycin Augments Immunomodulatory Properties of Bone Marrow-Derived Mesenchymal Stem Cells in Experimental Autoimmune Encephalomyelitis. *Mol. Neurobiol.* **2017**, *54*, 2445–2457. [[CrossRef](#)]
330. Donia, M.; Mangano, K.; Amoroso, A.; Mazzarino, M.C.; Imbesi, R.; Castrogiovanni, P.; Coco, M.; Meroni, P.; Nicoletti, F. Treatment with rapamycin ameliorates clinical and histological signs of protracted relapsing experimental allergic encephalomyelitis in Dark Agouti rats and induces expansion of peripheral CD4+CD25+Foxp3+ regulatory T cells. *J. Autoimmun.* **2009**, *33*, 135–140. [[CrossRef](#)]
331. Borim, P.A.; Mimura, L.A.N.; Zorzella-Pezavento, S.F.G.; Polonio, C.M.; Peron, J.P.S.; Sartori, A.; Fraga-Silva, T.F.C. Effect of Rapamycin on MOG-Reactive Immune Cells and Lipopolysaccharide-Activated Microglia: An In Vitro Approach for Screening New Therapies for Multiple Sclerosis. *J. Interferon Cytokine Res.* **2022**, *42*, 153–160. [[CrossRef](#)]
332. Zhang, G.; Yin, L.; Luo, Z.; Chen, X.; He, Y.; Yu, X.; Wang, M.; Tian, F.; Luo, H. Effects and potential mechanisms of rapamycin on MPTP-induced acute Parkinson's disease in mice. *Ann. Palliat. Med.* **2021**, *10*, 2889–2897. [[CrossRef](#)]
333. Currim, F.; Singh, J.; Shinde, A.; Gohel, D.; Roy, M.; Singh, K.; Shukla, S.; Mane, M.; Vasiyani, H.; Singh, R. Exosome Release Is Modulated by the Mitochondrial-Lysosomal Crosstalk in Parkinson's Disease Stress Conditions. *Mol. Neurobiol.* **2021**, *58*, 1819–1833. [[CrossRef](#)] [[PubMed](#)]
334. Pupyshev, A.B.; Tenditnik, M.V.; Ovsyukova, M.V.; Akopyan, A.A.; Dubrovina, N.I.; Tikhonova, M.A. Restoration of Parkinson's Disease-Like Deficits by Activating Autophagy through mTOR-Dependent and mTOR-Independent Mechanisms in Pharmacological and Transgenic Models of Parkinson's Disease in Mice. *Bull Exp. Biol. Med.* **2021**, *171*, 425–430. [[CrossRef](#)] [[PubMed](#)]
335. Guo, Q.; Wang, B.; Wang, X.; Smith, W.W.; Zhu, Y.; Liu, Z. Activation of Nrf2 in Astrocytes Suppressed PD-Like Phenotypes via Antioxidant and Autophagy Pathways in Rat and Drosophila Models. *Cells* **2021**, *10*, 1850. [[CrossRef](#)] [[PubMed](#)]
336. Srivastava, I.N.; Shperdheja, J.; Baybis, M.; Ferguson, T.; Crino, P.B. mTOR pathway inhibition prevents neuroinflammation and neuronal death in a mouse model of cerebral palsy. *Neurobiol. Dis.* **2016**, *85*, 144–154. [[CrossRef](#)] [[PubMed](#)]
337. Abdulrahman, B.A.; Tahir, W.; Doh-Ura, K.; Gilch, S.; Schatzl, H.M. Combining autophagy stimulators and cellulose ethers for therapy against prion disease. *Prion* **2019**, *13*, 185–196. [[CrossRef](#)] [[PubMed](#)]
338. Cortes, C.J.; Qin, K.; Cook, J.; Solanki, A.; Mastrianni, J.A. Rapamycin delays disease onset and prevents PrP plaque deposition in a mouse model of Gerstmann-Sträussler-Scheinker disease. *J. Neurosci.* **2012**, *32*, 12396–12405. [[CrossRef](#)] [[PubMed](#)]
339. Ishibashi, D.; Homma, T.; Nakagaki, T.; Fuse, T.; Sano, K.; Takatsuki, H.; Atarashi, R.; Nishida, N. Strain-Dependent Effect of Macroautophagy on Abnormally Folded Prion Protein Degradation in Infected Neuronal Cells. *PLoS ONE* **2015**, *10*, e0137958. [[CrossRef](#)]
340. Wang, H.; Fu, J.; Xu, X.; Yang, Z.; Zhang, T. Rapamycin Activates Mitophagy and Alleviates Cognitive and Synaptic Plasticity Deficits in a Mouse Model of Alzheimer's Disease. *J. Gerontol. A Biol. Sci. Med. Sci.* **2021**, *76*, 1707–1713. [[CrossRef](#)]
341. Pupyshev, A.B.; Belichenko, V.M.; Tenditnik, M.V.; Bashirzade, A.A.; Dubrovina, N.I.; Ovsyukova, M.V.; Akopyan, A.A.; Fedoseeva, L.A.; Korolenko, T.A.; Amstislavskaya, T.G.; et al. Combined induction of mTOR-dependent and mTOR-independent pathways of autophagy activation as an experimental therapy for Alzheimer's disease-like pathology in a mouse model. *Pharmacol. Biochem. Behav.* **2022**, *217*, 173406. [[CrossRef](#)]
342. Van Skike, C.E.; Hussong, S.A.; Hernandez, S.F.; Banh, A.Q.; DeRosa, N.; Galvan, V. mTOR Attenuation with Rapamycin Reverses Neurovascular Uncoupling and Memory Deficits in Mice Modeling Alzheimer's Disease. *J. Neurosci.* **2021**, *41*, 4305–4320. [[CrossRef](#)]
343. Kakoty, V.; Yang, C.H.; Kumari, S.; Dubey, S.K.; Taliyan, R. Neuroprotective Effect of Lentivirus-Mediated FGF21 Gene Delivery in Experimental Alzheimer's Disease is Augmented when Concerted with Rapamycin. *Mol. Neurobiol.* **2022**, *59*, 2659–2677. [[CrossRef](#)] [[PubMed](#)]
344. Lai, C.; Chen, Z.; Ding, Y.; Chen, Q.; Su, S.; Liu, H.; Ni, R.; Tang, Z. Rapamycin Attenuated Zinc-Induced Tau Phosphorylation and Oxidative Stress in Rats: Involvement of Dual mTOR/p70S6K and Nrf2/HO-1 Pathways. *Front. Immunol.* **2022**, *13*, 782434. [[CrossRef](#)] [[PubMed](#)]
345. Zheng, G.; Wang, L.; Li, X.; Niu, X.; Xu, G.; Lv, P. Rapamycin alleviates cognitive impairment in murine vascular dementia: The enhancement of mitophagy by PI3K/AKT/mTOR axis. *Tissue Cell* **2021**, *69*, 101481. [[CrossRef](#)] [[PubMed](#)]
346. Ding, Y.; Liu, H.; Cen, M.; Tao, Y.; Lai, C.; Tang, Z. Rapamycin Ameliorates Cognitive Impairments and Alzheimer's Disease-Like Pathology with Restoring Mitochondrial Abnormality in the Hippocampus of Streptozotocin-Induced Diabetic Mice. *Neurochem. Res.* **2021**, *46*, 265–275. [[CrossRef](#)] [[PubMed](#)]
347. Jiang, T.; Zhang, W.; Wang, Y.; Zhang, T.; Wang, H.; Yang, Z. Rapamycin Pretreatment Attenuates High Glucose-induced Alteration of Synaptic Transmission in Hippocampal Dentate Gyrus Neurons. *Neuroscience* **2022**, *490*, 182–192. [[CrossRef](#)]
348. Ravikumar, B.; Vacher, C.; Berger, Z.; Davies, J.E.; Luo, S.; Oroz, L.G.; Scaravilli, F.; Easton, D.F.; Duden, R.; O'Kane, C.J.; et al. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat. Genet.* **2004**, *36*, 585–595. [[CrossRef](#)]
349. King, M.A.; Hands, S.; Hafiz, F.; Mizushima, N.; Tolkovsky, A.M.; Wyttenbach, A. Rapamycin inhibits polyglutamine aggregation independently of autophagy by reducing protein synthesis. *Mol. Pharmacol.* **2008**, *73*, 1052–1063. [[CrossRef](#)]

350. Pereira, G.J.; Tressoldi, N.; Hirata, H.; Bincoletto, C.; Smaili, S.S. Autophagy as a neuroprotective mechanism against 3-nitropropionic acid-induced murine astrocyte cell death. *Neurochem. Res.* **2013**, *38*, 2418–2426. [[CrossRef](#)]
351. Sarkar, S.; Davies, J.E.; Huang, Z.; Tunnacliffe, A.; Rubinsztein, D.C. Trehalose, a novel mTOR-independent autophagy enhancer, accelerates the clearance of mutant huntingtin and alpha-synuclein. *J. Biol. Chem.* **2007**, *282*, 5641–5652. [[CrossRef](#)]
352. Chen, L.L.; Wu, J.C.; Wang, L.H.; Wang, J.; Qin, Z.H.; Difiglia, M.; Lin, F. Rapamycin prevents the mutant huntingtin-suppressed GLT-1 expression in cultured astrocytes. *Acta Pharmacol. Sin.* **2012**, *33*, 385–392. [[CrossRef](#)]
353. Sarkar, S.; Krishna, G.; Imarisio, S.; Saiki, S.; O’Kane, C.J.; Rubinsztein, D.C. A rational mechanism for combination treatment of Huntington’s disease using lithium and rapamycin. *Hum. Mol. Genet.* **2008**, *17*, 170–178. [[CrossRef](#)] [[PubMed](#)]
354. Kolosova, N.G.; Muraleva, N.A.; Zhdankina, A.A.; Stefanova, N.A.; Fursova, A.Z.; Blagosklonny, M.V. Prevention of age-related macular degeneration-like retinopathy by rapamycin in rats. *Am. J. Pathol.* **2012**, *181*, 472–477. [[CrossRef](#)] [[PubMed](#)]
355. Kitaoka, Y.; Munemasa, Y.; Kojima, K.; Hirano, A.; Ueno, S.; Takagi, H. Axonal protection by Nmnat3 overexpression with involvement of autophagy in optic nerve degeneration. *Cell Death Dis.* **2013**, *4*, e860. [[CrossRef](#)] [[PubMed](#)]
356. Russo, R.; Varano, G.P.; Adornetto, A.; Nazio, F.; Tettamanti, G.; Girardello, R.; Cianfanelli, V.; Cavaliere, F.; Morrone, L.A.; Corasaniti, M.T.; et al. Rapamycin and fasting sustain autophagy response activated by ischemia/reperfusion injury and promote retinal ganglion cell survival. *Cell Death Dis.* **2018**, *9*, 981. [[CrossRef](#)]
357. Xu, C.; Zhang, H.; Liu, C.; Zhu, Y.; Wang, X.; Gao, W.; Huang, S.; Chen, L. Rapamycin inhibits Erk1/2-mediated neuronal apoptosis caused by cadmium. *Oncotarget* **2015**, *6*, 21452–21467. [[CrossRef](#)]
358. Wang, T.; Yuan, Y.; Zou, H.; Yang, J.; Zhao, S.; Ma, Y.; Wang, Y.; Bian, J.; Liu, X.; Gu, J.; et al. The ER stress regulator Bip mediates cadmium-induced autophagy and neuronal senescence. *Sci. Rep.* **2016**, *6*, 38091. [[CrossRef](#)]
359. Xu, C.; Liu, C.; Liu, L.; Zhang, R.; Zhang, H.; Chen, S.; Luo, Y.; Chen, L.; Huang, S. Rapamycin prevents cadmium-induced neuronal cell death via targeting both mTORC1 and mTORC2 pathways. *Neuropharmacology* **2015**, *97*, 35–45. [[CrossRef](#)]
360. Xu, C.; Wang, X.; Zhu, Y.; Dong, X.; Liu, C.; Zhang, H.; Liu, L.; Huang, S.; Chen, L. Rapamycin ameliorates cadmium-induced activation of MAPK pathway and neuronal apoptosis by preventing mitochondrial ROS inactivation of PP2A. *Neuropharmacology* **2016**, *105*, 270–284. [[CrossRef](#)]
361. Guo, S.; Xu, N.; Chen, P.; Liu, Y.; Qi, X.; Liu, S.; Li, C.; Tang, J. Rapamycin Protects Spiral Ganglion Neurons from Gentamicin-Induced Degeneration In Vitro. *J. Assoc. Res. Otolaryngol.* **2019**, *20*, 475–487. [[CrossRef](#)]
362. Caccamo, A.; Magri, A.; Medina, D.X.; Wisely, E.V.; López-Aranda, M.F.; Silva, A.J.; Oddo, S. mTOR regulates tau phosphorylation and degradation: Implications for Alzheimer’s disease and other tauopathies. *Aging Cell* **2013**, *12*, 370–380. [[CrossRef](#)]
363. Ozcelik, S.; Fraser, G.; Castets, P.; Schaeffer, V.; Skachokova, Z.; Breu, K.; Clavaguera, F.; Sinnreich, M.; Kappos, L.; Goedert, M.; et al. Rapamycin attenuates the progression of tau pathology in P301S tau transgenic mice. *PLoS ONE* **2013**, *8*, e62459. [[CrossRef](#)] [[PubMed](#)]
364. Cullen, V.; Sardi, S.P.; Ng, J.; Xu, Y.H.; Sun, Y.; Tomlinson, J.J.; Kolodziej, P.; Kahn, I.; Saftig, P.; Woulfe, J.; et al. Acid  $\beta$ -glucosidase mutants linked to Gaucher disease, Parkinson disease, and Lewy body dementia alter  $\alpha$ -synuclein processing. *Ann. Neurol.* **2011**, *69*, 940–953. [[CrossRef](#)] [[PubMed](#)]
365. Hoffmann, A.C.; Minakaki, G.; Menges, S.; Salvi, R.; Savitskiy, S.; Kazman, A.; Vicente Miranda, H.; Mielenz, D.; Klucken, J.; Winkler, J.; et al. Extracellular aggregated alpha synuclein primarily triggers lysosomal dysfunction in neural cells prevented by trehalose. *Sci. Rep.* **2019**, *9*, 544. [[CrossRef](#)] [[PubMed](#)]
366. Rockenstein, E.; Ostroff, G.; Dikengil, F.; Rus, F.; Mante, M.; Florio, J.; Adame, A.; Trinh, I.; Kim, C.; Overk, C.; et al. Combined Active Humoral and Cellular Immunization Approaches for the Treatment of Synucleinopathies. *J. Neurosci.* **2018**, *38*, 1000–1014. [[CrossRef](#)]
367. Jing, F.; Yang, F.; Cui, F.; Chen, Z.; Ling, L.; Huang, X. Rapamycin alleviates inflammation and muscle weakness, while altering the Treg/Th17 balance in a rat model of myasthenia gravis. *Biosci. Rep.* **2017**, *37*, BSR20170767. [[CrossRef](#)]
368. Gao, X.; Wen, Y.; Wang, Z.; Wang, G.; Guo, J.; Yu, L.; Wang, Z. Rapamycin alleviates the symptoms of experimental autoimmune myasthenia gravis rats by down-regulating Th17 cell/regulatory T cell ratio. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* **2021**, *37*, 24–30.
369. Uberti, V.H.; de Freitas, B.S.; Molz, P.; Bromberg, E.; Schröder, N. Iron Overload Impairs Autophagy: Effects of Rapamycin in Ameliorating Iron-Related Memory Deficits. *Mol. Neurobiol.* **2020**, *57*, 1044–1054. [[CrossRef](#)]
370. Zhang, C.Q.; Yi, S.; Chen, B.B.; Cui, P.P.; Wang, Y.; Li, Y.Z. mTOR/NF- $\kappa$ B signaling pathway protects hippocampal neurons from injury induced by intermittent hypoxia in rats. *Int. J. Neurosci.* **2021**, *131*, 994–1003. [[CrossRef](#)]
371. Sabran-Cohen, T.; Bright, U.; Mizrahi Zer-Aviv, T.; Akirav, I. Rapamycin prevents the long-term impairing effects of adolescence  $\Delta$ -9-tetrahydrocannabinol on memory and plasticity in male rats. *Eur. J. Neurosci.* **2021**, *54*, 6104–6122. [[CrossRef](#)]
372. Chen, X.; Gao, F.; Lin, C.; Chen, A.; Deng, J.; Chen, P.; Lin, M.; Xie, B.; Liao, Y.; Gong, C.; et al. mTOR-mediated autophagy in the hippocampus is involved in perioperative neurocognitive disorders in diabetic rats. *CNS Neurosci. Ther.* **2022**, *28*, 540–553. [[CrossRef](#)]
373. Chen, G.; Ke, Z.; Xu, M.; Liao, M.; Wang, X.; Qi, Y.; Zhang, T.; Frank, J.A.; Bower, K.A.; Shi, X.; et al. Autophagy is a protective response to ethanol neurotoxicity. *Autophagy* **2012**, *8*, 1577–1589. [[CrossRef](#)] [[PubMed](#)]
374. Yang, N.; Liu, X.; Niu, X.; Wang, X.; Jiang, R.; Yuan, N.; Wang, J.; Zhang, C.; Lim, K.L.; Lu, L. Activation of Autophagy Ameliorates Age-Related Neurogenesis Decline and Neurodysfunction in Adult Mice. *Stem Cell Rev. Rep.* **2022**, *18*, 626–641. [[CrossRef](#)] [[PubMed](#)]



375. Ni, L.; Wei, Y.; Pan, J.; Li, X.; Xu, B.; Deng, Y.; Yang, T.; Liu, W. The effects of mTOR or Vps34-mediated autophagy on methylmercury-induced neuronal apoptosis in rat cerebral cortex. *Food Chem. Toxicol.* **2021**, *155*, 112386. [[CrossRef](#)] [[PubMed](#)]
376. Caccamo, A.; Majumder, S.; Deng, J.J.; Bai, Y.; Thornton, F.B.; Oddo, S. Rapamycin rescues TDP-43 mislocalization and the associated low molecular mass neurofilament instability. *J. Biol. Chem.* **2009**, *284*, 27416–27424. [[CrossRef](#)] [[PubMed](#)]
377. Chennampally, P.; Sayed-Zahid, A.; Soundararajan, P.; Sharp, J.; Cox, G.A.; Collins, S.D.; Smith, R.L. A microfluidic approach to rescue ALS motor neuron degeneration using rapamycin. *Sci. Rep.* **2021**, *11*, 18168. [[CrossRef](#)]
378. Tsai, P.T.; Rudolph, S.; Guo, C.; Ellegood, J.; Gibson, J.M.; Schaeffer, S.M.; Mogavero, J.; Lerch, J.P.; Regehr, W.; Sahin, M. Sensitive Periods for Cerebellar-Mediated Autistic-like Behaviors. *Cell Rep.* **2018**, *25*, 357–367.e4. [[CrossRef](#)]
379. Kotajima-Murakami, H.; Kobayashi, T.; Kashii, H.; Sato, A.; Hagino, Y.; Tanaka, M.; Nishito, Y.; Takamatsu, Y.; Uchino, S.; Ikeda, K. Effects of rapamycin on social interaction deficits and gene expression in mice exposed to valproic acid in utero. *Mol. Brain* **2019**, *12*, 3. [[CrossRef](#)]
380. McMahon, J.J.; Yu, W.; Yang, J.; Feng, H.; Helm, M.; McMahon, E.; Zhu, X.; Shin, D.; Huang, Y. Seizure-dependent mTOR activation in 5-HT neurons promotes autism-like behaviors in mice. *Neurobiol. Dis.* **2015**, *73*, 296–306. [[CrossRef](#)]
381. Burket, J.A.; Benson, A.D.; Tang, A.H.; Deutsch, S.I. Rapamycin improves sociability in the BTBR T(+)Itpr3(tf)/J mouse model of autism spectrum disorders. *Brain Res. Bull.* **2014**, *100*, 70–75. [[CrossRef](#)]
382. Xing, X.; Zhang, J.; Wu, K.; Cao, B.; Li, X.; Jiang, F.; Hu, Z.; Xia, K.; Li, J.D. Suppression of Akt-mTOR pathway rescued the social behavior in Cntnap2-deficient mice. *Sci. Rep.* **2019**, *9*, 3041. [[CrossRef](#)]
383. Wu, J.; de Theije, C.G.; da Silva, S.L.; van der Horst, H.; Reinders, M.T.; Broersen, L.M.; Willemsen, L.E.; Kas, M.J.; Garssen, J.; Kraneveld, A.D. mTOR plays an important role in cow's milk allergy-associated behavioral and immunological deficits. *Neuropharmacology* **2015**, *97*, 220–232. [[CrossRef](#)] [[PubMed](#)]
384. Xie, J.; Han, Q.; Wei, Z.; Wang, Y.; Wang, S.; Chen, M. Phenanthrene induces autism-like behavior by promoting oxidative stress and mTOR pathway activation. *Toxicology* **2021**, *461*, 152910. [[CrossRef](#)] [[PubMed](#)]
385. Amegandjin, C.A.; Choudhury, M.; Jadhav, V.; Carriço, J.N.; Quintal, A.; Berryer, M.; Snappyan, M.; Chattopadhyaya, B.; Saghatelian, A.; Di Cristo, G. Sensitive period for rescuing parvalbumin interneurons connectivity and social behavior deficits caused by TSC1 loss. *Nat. Commun.* **2021**, *12*, 3653. [[CrossRef](#)] [[PubMed](#)]
386. Del Grosso, A.; Angella, L.; Tonazzini, I.; Moscardini, A.; Giordano, N.; Caleo, M.; Rocchiccioli, S.; Cecchini, M. Dysregulated autophagy as a new aspect of the molecular pathogenesis of Krabbe disease. *Neurobiol. Dis.* **2019**, *129*, 195–207. [[CrossRef](#)]
387. Di Domenico, F.; Tramutola, A.; Barone, E.; Lanzillotta, C.; Defever, O.; Arena, A.; Zuliani, I.; Foppoli, C.; Iavarone, F.; Vincenzoni, F.; et al. Restoration of aberrant mTOR signaling by intranasal rapamycin reduces oxidative damage: Focus on HNE-modified proteins in a mouse model of down syndrome. *Redox Biol.* **2019**, *23*, 101162. [[CrossRef](#)]
388. Andrade-Talavera, Y.; Benito, I.; Casañas, J.J.; Rodríguez-Moreno, A.; Montesinos, M.L. Rapamycin restores BDNF-LTP and the persistence of long-term memory in a model of Down's syndrome. *Neurobiol. Dis.* **2015**, *82*, 516–525. [[CrossRef](#)] [[PubMed](#)]
389. Troca-Marín, J.A.; Alves-Sampaio, A.; Montesinos, M.L. An increase in basal BDNF provokes hyperactivation of the Akt-mammalian target of rapamycin pathway and deregulation of local dendritic translation in a mouse model of Down's syndrome. *J. Neurosci.* **2011**, *31*, 9445–9455. [[CrossRef](#)]
390. Urbano-Gómez, J.D.; Casañas, J.J.; Benito, I.; Montesinos, M.L. Prenatal treatment with rapamycin restores enhanced hippocampal mGluR-LTD and mushroom spine size in a Down's syndrome mouse model. *Mol. Brain* **2021**, *14*, 84. [[CrossRef](#)]
391. Reijnders, M.R.F.; Kousi, M.; van Woerden, G.M.; Klein, M.; Bralten, J.; Mancini, G.M.S.; van Essen, T.; Proietti-Onori, M.; Smeets, E.E.J.; van Gastel, M.; et al. Variation in a range of mTOR-related genes associates with intracranial volume and intellectual disability. *Nat. Commun.* **2017**, *8*, 1052. [[CrossRef](#)]
392. Lopatynska-Mazurek, M.; Antolak, A.; Grochecki, P.; Gibula-Tarlowska, E.; Bodzon-Kulakowska, A.; Listos, J.; Kedzierska, E.; Suder, P.; Silberring, J.; Kotlinska, J.H. Rapamycin Improves Spatial Learning Deficits, Vulnerability to Alcohol Addiction and Altered Expression of the GluN2B Subunit of the NMDA Receptor in Adult Rats Exposed to Ethanol during the Neonatal Period. *Biomolecules* **2021**, *11*, 650. [[CrossRef](#)]
393. Lopatynska-Mazurek, M.; Pankowska, A.; Gibula-Tarlowska, E.; Pietura, R.; Kotlinska, J.H. Rapamycin Improves Recognition Memory and Normalizes Amino-Acids and Amines Levels in the Hippocampal Dentate Gyrus in Adult Rats Exposed to Ethanol during the Neonatal Period. *Biomolecules* **2021**, *11*, 362. [[CrossRef](#)] [[PubMed](#)]
394. Lopatynska-Mazurek, M.; Komsta, L.; Gibula-Tarlowska, E.; Kotlinska, J.H. Aversive Learning Deficits and Depressive-Like Behaviors Are Accompanied by an Increase in Oxidative Stress in a Rat Model of Fetal Alcohol Spectrum Disorders: The Protective Effect of Rapamycin. *Int. J. Mol. Sci.* **2021**, *22*, 7083. [[CrossRef](#)] [[PubMed](#)]
395. Chi, O.Z.; Wu, C.C.; Liu, X.; Rah, K.H.; Jacinto, E.; Weiss, H.R. Restoration of Normal Cerebral Oxygen Consumption with Rapamycin Treatment in a Rat Model of Autism-Tuberous Sclerosis. *Neuromolecular Med.* **2015**, *17*, 305–313. [[CrossRef](#)] [[PubMed](#)]
396. Tang, G.; Gudsruk, K.; Kuo, S.H.; Cotrina, M.L.; Rosoklija, G.; Sosunov, A.; Sonders, M.S.; Kanter, E.; Castagna, C.; Yamamoto, A.; et al. Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. *Neuron* **2014**, *83*, 1131–1143. [[CrossRef](#)]
397. Tsai, P.T.; Hull, C.; Chu, Y.; Greene-Colozzi, E.; Sadowski, A.R.; Leech, J.M.; Steinberg, J.; Crawley, J.N.; Regehr, W.G.; Sahin, M. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature* **2012**, *488*, 647–651. [[CrossRef](#)]
398. Sato, A.; Kasai, S.; Kobayashi, T.; Takamatsu, Y.; Hino, O.; Ikeda, K.; Mizuguchi, M. Rapamycin reverses impaired social interaction in mouse models of tuberous sclerosis complex. *Nat. Commun.* **2012**, *3*, 1292. [[CrossRef](#)]

399. Carson, R.P.; Van Nielen, D.L.; Winzenburger, P.A.; Ess, K.C. Neuronal and glia abnormalities in Tsc1-deficient forebrain and partial rescue by rapamycin. *Neurobiol. Dis.* **2012**, *45*, 369–380. [[CrossRef](#)]
400. Meikle, L.; Pollizzi, K.; Egnor, A.; Kramvis, I.; Lane, H.; Sahin, M.; Kwiatkowski, D.J. Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: Effects on mTORC1 and Akt signaling lead to improved survival and function. *J. Neurosci.* **2008**, *28*, 5422–5432. [[CrossRef](#)]
401. Sundberg, M.; Tochitsky, I.; Buchholz, D.E.; Winden, K.; Kujala, V.; Kapur, K.; Cataltepe, D.; Turner, D.; Han, M.J.; Woolf, C.J.; et al. Purkinje cells derived from TSC patients display hypoexcitability and synaptic deficits associated with reduced FMRP levels and reversed by rapamycin. *Mol. Psychiatry* **2018**, *23*, 2167–2183. [[CrossRef](#)]
402. Way, S.W.; Rozas, N.S.; Wu, H.C.; McKenna, J., 3rd; Reith, R.M.; Hashmi, S.S.; Dash, P.K.; Gambello, M.J. The differential effects of prenatal and/or postnatal rapamycin on neurodevelopmental defects and cognition in a neuroglial mouse model of tuberous sclerosis complex. *Hum. Mol. Genet.* **2012**, *21*, 3226–3236. [[CrossRef](#)]
403. Martin, P.; Wagh, V.; Reis, S.A.; Erdin, S.; Beauchamp, R.L.; Shaikh, G.; Talkowski, M.; Thiele, E.; Sheridan, S.D.; Haggarty, S.J.; et al. TSC patient-derived isogenic neural progenitor cells reveal altered early neurodevelopmental phenotypes and rapamycin-induced MNK-eIF4E signaling. *Mol. Autism* **2020**, *11*, 2. [[CrossRef](#)] [[PubMed](#)]
404. Ehninger, D.; Han, S.; Shilyansky, C.; Zhou, Y.; Li, W.; Kwiatkowski, D.J.; Ramesh, V.; Silva, A.J. Reversal of learning deficits in a Tsc2+/- mouse model of tuberous sclerosis. *Nat. Med.* **2008**, *14*, 843–848. [[CrossRef](#)] [[PubMed](#)]
405. Cambiaghi, M.; Cursi, M.; Magri, L.; Castoldi, V.; Comi, G.; Minicucci, F.; Galli, R.; Leocani, L. Behavioural and EEG effects of chronic rapamycin treatment in a mouse model of tuberous sclerosis complex. *Neuropharmacology* **2013**, *67*, 1–7. [[CrossRef](#)] [[PubMed](#)]
406. Parker, W.E.; Orlova, K.A.; Parker, W.H.; Birnbaum, J.F.; Krymskaya, V.P.; Goncharov, D.A.; Baybis, M.; Helfferich, J.; Okochi, K.; Strauss, K.A.; et al. Rapamycin prevents seizures after depletion of STRADA in a rare neurodevelopmental disorder. *Sci. Transl. Med.* **2013**, *5*, 182ra53. [[CrossRef](#)] [[PubMed](#)]
407. Zhong, S.; Zhao, Z.; Xie, W.; Cai, Y.; Zhang, Y.; Ding, J.; Wang, X. GABAergic Interneuron and Neurotransmission Are mTOR-Dependently Disturbed in Experimental Focal Cortical Dysplasia. *Mol. Neurobiol.* **2021**, *58*, 156–169. [[CrossRef](#)] [[PubMed](#)]
408. Akman, O.; Briggs, S.W.; Mowrey, W.B.; Moshé, S.L.; Galanopoulou, A.S. Antiepileptogenic effects of rapamycin in a model of infantile spasms due to structural lesions. *Epilepsia* **2021**, *62*, 1985–1999. [[CrossRef](#)]
409. Ishida, S.; Zhao, D.; Sawada, Y.; Hiraoka, Y.; Mashimo, T.; Tanaka, K. Dorsal telencephalon-specific Nprl2- and Nprl3-knockout mice: Novel mouse models for GATORopathy. *Hum. Mol. Genet.* **2022**, *31*, 1519–1530. [[CrossRef](#)]
410. Aghaie, F.; Moradifar, F.; Hosseini, A. Rapamycin attenuates depression and anxiety-like behaviors through modulation of the NLRP3 pathway in pentylenetetrazole-kindled male Wistar rats. *Fundam. Clin. Pharmacol.* **2021**, *35*, 1045–1054. [[CrossRef](#)]
411. Crutcher, E.; Pal, R.; Naini, F.; Zhang, P.; Laugsch, M.; Kim, J.; Bajic, A.; Schaaf, C.P. mTOR and autophagy pathways are dysregulated in murine and human models of Schaaf-Yang syndrome. *Sci. Rep.* **2019**, *9*, 15935. [[CrossRef](#)]
412. Gordon, E.B.; Hart, G.T.; Tran, T.M.; Waisberg, M.; Akkaya, M.; Skinner, J.; Zinöcker, S.; Pena, M.; Yazew, T.; Qi, C.F.; et al. Inhibiting the Mammalian target of rapamycin blocks the development of experimental cerebral malaria. *mBio* **2015**, *6*, e00725. [[CrossRef](#)]
413. Mejia, P.; Treviño-Villarreal, J.H.; Reynolds, J.S.; De Niz, M.; Thompson, A.; Marti, M.; Mitchell, J.R. A single rapamycin dose protects against late-stage experimental cerebral malaria via modulation of host immunity, endothelial activation and parasite sequestration. *Malar. J.* **2017**, *16*, 455. [[CrossRef](#)] [[PubMed](#)]
414. Mejia, P.; Treviño-Villarreal, J.H.; Hine, C.; Harputlugil, E.; Lang, S.; Calay, E.; Rogers, R.; Wirth, D.; Duraisingh, M.T.; Mitchell, J.R. Dietary restriction protects against experimental cerebral malaria via leptin modulation and T-cell mTORC1 suppression. *Nat. Commun.* **2015**, *6*, 6050. [[CrossRef](#)] [[PubMed](#)]
415. Hu, J.; Chen, X.; Cheng, J.; Kong, F.; Xia, H.; Wu, J. Mammalian target of rapamycin signaling pathway is involved in synaptic plasticity of the spinal dorsal horn and neuropathic pain in rats by regulating autophagy. *Neuroreport* **2021**, *32*, 925–935. [[CrossRef](#)] [[PubMed](#)]
416. Liu, F.; Wu, M.; Kai, J.; Dong, J.; Zhang, B.; Liu, L.; Zhu, F.; Zeng, L.H. Effectiveness of low dose of rapamycin in preventing seizure-induced anxiety-like behaviour, cognitive impairment, and defects in neurogenesis in developing rats. *Int. J. Neurosci.* **2020**, *130*, 9–18. [[CrossRef](#)]
417. Li, Y.; Cheng, Y.; Zhou, Y.; Du, H.; Zhang, C.; Zhao, Z.; Chen, Y.; Zhou, Z.; Mei, J.; Wu, W.; et al. High fat diet-induced obesity leads to depressive and anxiety-like behaviors in mice via AMPK/mTOR-mediated autophagy. *Exp. Neurol.* **2022**, *348*, 113949. [[CrossRef](#)]
418. Felici, R.; Buonvicino, D.; Muzzi, M.; Cavone, L.; Guasti, D.; Lapucci, A.; Pratesi, S.; De Cesaris, F.; Luceri, F.; Chiarugi, A. Post onset, oral rapamycin treatment delays development of mitochondrial encephalopathy only at supra-maximal doses. *Neuropharmacology* **2017**, *117*, 74–84. [[CrossRef](#)]
419. Wang, S.; Zhou, S.L.; Min, F.Y.; Ma, J.J.; Shi, X.J.; Berezcki, E.; Wu, J. mTOR-mediated hyperphosphorylation of tau in the hippocampus is involved in cognitive deficits in streptozotocin-induced diabetic mice. *Metab. Brain Dis.* **2014**, *29*, 729–736. [[CrossRef](#)]
420. Sun, Q.; Wei, L.L.; Zhang, M.; Li, T.X.; Yang, C.; Deng, S.P.; Zeng, Q.C. Rapamycin inhibits activation of AMPK-mTOR signaling pathway-induced Alzheimer's disease lesion in hippocampus of rats with type 2 diabetes mellitus. *Int. J. Neurosci.* **2019**, *129*, 179–188. [[CrossRef](#)]



421. Xu, T.; Liu, J.; Li, X.R.; Yu, Y.; Luo, X.; Zheng, X.; Cheng, Y.; Yu, P.Q.; Liu, Y. The mTOR/NF- $\kappa$ B Pathway Mediates Neuroinflammation and Synaptic Plasticity in Diabetic Encephalopathy. *Mol. Neurobiol.* **2021**, *58*, 3848–3862. [[CrossRef](#)]
422. Gao, Y.; Peng, S.; Wen, Q.; Zheng, C.; Lin, J.; Tan, Y.; Ma, Y.; Luo, Y.; Xue, Y.; Wu, P.; et al. The mammalian target of rapamycin pathway in the basolateral amygdala is critical for nicotine-induced behavioural sensitization. *Int. J. Neuropsychopharmacol.* **2014**, *17*, 1881–1894. [[CrossRef](#)]
423. Zhou, Y.; Liang, Y.; Kreek, M.J. mTORC1 pathway is involved in the kappa opioid receptor activation-induced increase in excessive alcohol drinking in mice. *Pharmacol. Biochem. Behav.* **2020**, *195*, 172954. [[CrossRef](#)] [[PubMed](#)]
424. Barak, S.; Liu, F.; Ben Hamida, S.; Yowell, Q.V.; Neasta, J.; Kharazia, V.; Janak, P.H.; Ron, D. Disruption of alcohol-related memories by mTORC1 inhibition prevents relapse. *Nat. Neurosci.* **2013**, *16*, 1111–1117. [[CrossRef](#)] [[PubMed](#)]
425. Canivet, C.; Menasria, R.; Rhéaume, C.; Piret, J.; Boivin, G. Valacyclovir combined with artesunate or rapamycin improves the outcome of herpes simplex virus encephalitis in mice compared to antiviral therapy alone. *Antiviral Res.* **2015**, *123*, 105–113. [[CrossRef](#)]
426. Cleary, C.; Linde, J.A.; Hiscock, K.M.; Hadas, I.; Belmaker, R.H.; Agam, G.; Flaisher-Grinberg, S.; Einat, H. Antidepressive-like effects of rapamycin in animal models: Implications for mTOR inhibition as a new target for treatment of affective disorders. *Brain Res. Bull.* **2008**, *76*, 469–473. [[CrossRef](#)] [[PubMed](#)]
427. Kara, N.Z.; Flaisher-Grinberg, S.; Anderson, G.W.; Agam, G.; Einat, H. Mood-stabilizing effects of rapamycin and its analog temsirolimus: Relevance to autophagy. *Behav. Pharmacol.* **2018**, *29*, 379–384. [[CrossRef](#)]
428. Ding, N.; Zhao, K.; Lan, Y.; Li, Z.; Lv, X.; Su, J.; Lu, H.; Gao, F.; He, W. Induction of Atypical Autophagy by Porcine Hemagglutinating Encephalomyelitis Virus Contributes to Viral Replication. *Front. Cell. Infect. Microbiol.* **2017**, *7*, 56. [[CrossRef](#)] [[PubMed](#)]
429. Blundell, J.; Kouser, M.; Powell, C.M. Systemic inhibition of mammalian target of rapamycin inhibits fear memory reconsolidation. *Neurobiol. Learn. Mem.* **2008**, *90*, 28–35. [[CrossRef](#)]
430. Fifield, K.; Hebert, M.; Angel, R.; Adamec, R.; Blundell, J. Inhibition of mTOR kinase via rapamycin blocks persistent predator stress-induced hyperarousal. *Behav. Brain Res.* **2013**, *256*, 457–463. [[CrossRef](#)]
431. Levin, N.; Kritman, M.; Maroun, M.; Akirav, I. Differential roles of the infralimbic and prelimbic areas of the prefrontal cortex in reconsolidation of a traumatic memory. *Eur. Neuropsychopharmacol.* **2017**, *27*, 900–912. [[CrossRef](#)]
432. Li, G.Y.; Fan, B.; Jiao, Y.Y. Rapamycin attenuates visible light-induced injury in retinal photoreceptor cells via inhibiting endoplasmic reticulum stress. *Brain Res.* **2014**, *1563*, 1–12. [[CrossRef](#)]
433. Nalbandian, A.; Llewellyn, K.J.; Nguyen, C.; Yazdi, P.G.; Kimonis, V.E. Rapamycin and chloroquine: The in vitro and in vivo effects of autophagy-modifying drugs show promising results in valosin containing protein multisystem proteinopathy. *PLoS ONE* **2015**, *10*, e0122888. [[CrossRef](#)] [[PubMed](#)]
434. Hayashi, I.; Aoki, Y.; Ushikubo, H.; Asano, D.; Mori, A.; Sakamoto, K.; Nakahara, T.; Ishii, K. Protective effects of PF-4708671 against N-methyl-D-aspartic acid-induced retinal damage in rats. *Fundam. Clin. Pharmacol.* **2016**, *30*, 529–536. [[CrossRef](#)]
435. Ichikawa, A.; Nakahara, T.; Kurauchi, Y.; Mori, A.; Sakamoto, K.; Ishii, K. Rapamycin prevents N-methyl-D-aspartate-induced retinal damage through an ERK-dependent mechanism in rats. *J. Neurosci. Res.* **2014**, *92*, 692–702. [[CrossRef](#)] [[PubMed](#)]
436. Aoki, Y.; Nakahara, T.; Asano, D.; Ushikubo, H.; Mori, A.; Sakamoto, K.; Ishii, K. Preventive effects of rapamycin on inflammation and capillary degeneration in a rat model of NMDA-induced retinal injury. *Biol. Pharm. Bull.* **2015**, *38*, 321–324. [[CrossRef](#)] [[PubMed](#)]
437. Ying, H.; Turturro, S.; Nguyen, T.; Shen, X.; Zelkha, R.; Johnson, E.C.; Morrison, J.C.; Yue, B.Y. Induction of autophagy in rats upon overexpression of wild-type and mutant optineurin gene. *BMC Cell Biol.* **2015**, *16*, 14. [[CrossRef](#)] [[PubMed](#)]
438. Foerster, P.; Daclin, M.; Asm, S.; Faucourt, M.; Boletta, A.; Genovesio, A.; Spassky, N. mTORC1 signaling and primary cilia are required for brain ventricle morphogenesis. *Development* **2017**, *144*, 201–210. [[CrossRef](#)]
439. Metaxakis, A.; Tain, L.S.; Grönke, S.; Hendrich, O.; Hinze, Y.; Birras, U.; Partridge, L. Lowered insulin signalling ameliorates age-related sleep fragmentation in Drosophila. *PLoS Biol.* **2014**, *12*, e1001824. [[CrossRef](#)]
440. Liu, W.; Guo, J.; Mu, J.; Tian, L.; Zhou, D. Rapamycin Protects Sepsis-Induced Cognitive Impairment in Mouse Hippocampus by Enhancing Autophagy. *Cell Mol. Neurobiol.* **2017**, *37*, 1195–1205. [[CrossRef](#)]
441. James, M.H.; Quinn, R.K.; Ong, L.K.; Levi, E.M.; Charnley, J.L.; Smith, D.W.; Dickson, P.W.; Dayas, C.V. mTORC1 inhibition in the nucleus accumbens ‘protects’ against the expression of drug seeking and ‘relapse’ and is associated with reductions in GluA1 AMPAR and CAMKII $\alpha$  levels. *Neuropsychopharmacology* **2014**, *39*, 1694–1702. [[CrossRef](#)]
442. James, M.H.; Quinn, R.K.; Ong, L.K.; Levi, E.M.; Smith, D.W.; Dickson, P.W.; Dayas, C.V. Rapamycin reduces motivated responding for cocaine and alters GluA1 expression in the ventral but not dorsal striatum. *Eur. J. Pharmacol.* **2016**, *784*, 147–154. [[CrossRef](#)]
443. Bailey, J.; Ma, D.; Szumlinski, K.K. Rapamycin attenuates the expression of cocaine-induced place preference and behavioral sensitization. *Addict. Biol.* **2012**, *17*, 248–258. [[CrossRef](#)]
444. Towner, R.A.; Gulej, R.; Zalles, M.; Saunders, D.; Smith, N.; Lerner, M.; Morton, K.A.; Richardson, A. Rapamycin restores brain vasculature, metabolism, and blood-brain barrier in an inflammaging model. *Geroscience* **2021**, *43*, 563–578. [[CrossRef](#)]
445. Linda, K.; Lewerissa, E.I.; Verboven, A.H.A.; Gabriele, M.; Frega, M.; Klein Gunnewiek, T.M.; Devilee, L.; Ulferts, E.; Hommersom, M.; Oudakker, A.; et al. Imbalanced autophagy causes synaptic deficits in a human model for neurodevelopmental disorders. *Autophagy* **2022**, *18*, 423–442. [[CrossRef](#)]

446. Kim, S.G.; Lee, S.; Kim, Y.; Park, J.; Woo, D.; Kim, D.; Li, Y.; Shin, W.; Kang, H.; Yook, C.; et al. Tanc2-mediated mTOR inhibition balances mTORC1/2 signaling in the developing mouse brain and human neurons. *Nat. Commun.* **2021**, *12*, 2695. [[CrossRef](#)]
447. Wen, J.; Xu, J.; Mathena, R.P.; Choi, J.H.; Mintz, C.D. Early Isoflurane Exposure Impairs Synaptic Development in Fmr1 KO Mice via the mTOR Pathway. *Neurochem. Res.* **2021**, *46*, 1577–1588. [[CrossRef](#)]
448. Tian, J.; Wang, Z.; Ren, Y.; Jiang, Y.; Zhao, Y.; Li, M.; Zhang, Z. Rapamycin Attenuates Anxiety and Depressive Behavior Induced by Helicobacter pylori in Association with Reduced Circulating Levels of Ghrelin. *Neural Plast* **2022**, *2022*, 2847672. [[CrossRef](#)]
449. Liu, H.; Li, F.; Li, X.; Wu, Q.; Dai, C. Rapamycin ameliorates age-related hearing loss in C57BL/6J mice by enhancing autophagy in the SGNs. *Neurosci. Lett.* **2022**, *772*, 136493. [[CrossRef](#)]
450. Zhang, J.; Xu, X.; Zhou, D.; Li, H.; You, W.; Wang, Z.; Chen, G. Possible Role of Raf-1 Kinase in the Development of Cerebral Vasospasm and Early Brain Injury After Experimental Subarachnoid Hemorrhage in Rats. *Mol. Neurobiol.* **2015**, *52*, 1527–1539. [[CrossRef](#)]
451. Hsieh, C.H.; Lin, Y.J.; Chen, W.L.; Huang, Y.C.; Chang, C.W.; Cheng, F.C.; Liu, R.S.; Shyu, W.C. HIF-1 $\alpha$  triggers long-lasting glutamate excitotoxicity via system x(c)(-) in cerebral ischaemia-reperfusion. *J. Pathol.* **2017**, *241*, 337–349. [[CrossRef](#)]
452. Wang, T.; Li, B.; Wang, Z.; Wang, X.; Xia, Z.; Ning, G.; Wang, X.; Zhang, Y.; Cui, L.; Yu, M.; et al. Sorafenib promotes sensory conduction function recovery via miR-142-3p/AC9/cAMP axis post dorsal column injury. *Neuropharmacology* **2019**, *148*, 347–357. [[CrossRef](#)]
453. Echeverria, V.; Burgess, S.; Gamble-George, J.; Zeitlin, R.; Lin, X.; Cao, C.; Arendash, G.W. Sorafenib inhibits nuclear factor kappa B, decreases inducible nitric oxide synthase and cyclooxygenase-2 expression, and restores working memory in APPswe mice. *Neuroscience* **2009**, *162*, 1220–1231. [[CrossRef](#)] [[PubMed](#)]
454. Kim, J.; Park, J.H.; Park, S.K.; Hoe, H.S. Sorafenib Modulates the LPS- and A $\beta$ -Induced Neuroinflammatory Response in Cells, Wild-Type Mice, and 5xFAD Mice. *Front. Immunol.* **2021**, *12*, 684344. [[CrossRef](#)] [[PubMed](#)]
455. Liu, Z.; Hamamichi, S.; Lee, B.D.; Yang, D.; Ray, A.; Caldwell, G.A.; Caldwell, K.A.; Dawson, T.M.; Smith, W.W.; Dawson, V.L. Inhibitors of LRRK2 kinase attenuate neurodegeneration and Parkinson-like phenotypes in Caenorhabditis elegans and Drosophila Parkinson's disease models. *Hum. Mol. Genet.* **2011**, *20*, 3933–3942. [[CrossRef](#)]
456. Moawad, E.Y. Induction of multiple sclerosis and response to tyrosine kinase inhibitors. *Indian J. Clin. Biochem.* **2014**, *29*, 491–495. [[CrossRef](#)]
457. Crespo, O.; Kang, S.C.; Daneman, R.; Lindstrom, T.M.; Ho, P.P.; Sobel, R.A.; Steinman, L.; Robinson, W.H. Tyrosine kinase inhibitors ameliorate autoimmune encephalomyelitis in a mouse model of multiple sclerosis. *J. Clin. Immunol.* **2011**, *31*, 1010–1020. [[CrossRef](#)] [[PubMed](#)]
458. Martina, B.E.E.; Smreczak, M.; Orłowska, A.; Marzec, A.; Trebas, P.; Roose, J.M.; Zmudzinski, J.; Gerhauser, I.; Wohlsein, P.; Baumgärtner, W.; et al. Combination drug treatment prolongs survival of experimentally infected mice with silver-haired bat rabies virus. *Vaccine* **2019**, *37*, 4736–4742. [[CrossRef](#)]
459. Brahms, A.; Mudhasani, R.; Pinkham, C.; Kota, K.; Nasar, F.; Zamani, R.; Bavari, S.; Kehn-Hall, K. Sorafenib Impedes Rift Valley Fever Virus Egress by Inhibiting Valosin-Containing Protein Function in the Cellular Secretory Pathway. *J. Virol.* **2017**, *91*, e00968-17. [[CrossRef](#)]
460. Lundberg, L.; Brahms, A.; Hooper, I.; Carey, B.; Lin, S.C.; Dahal, B.; Narayanan, A.; Kehn-Hall, K. Repurposed FDA-Approved drug sorafenib reduces replication of Venezuelan equine encephalitis virus and other alphaviruses. *Antivir. Res.* **2018**, *157*, 57–67. [[CrossRef](#)]
461. Gao, M.; Duan, H.; Liu, J.; Zhang, H.; Wang, X.; Zhu, M.; Guo, J.; Zhao, Z.; Meng, L.; Peng, Y. The multi-targeted kinase inhibitor sorafenib inhibits enterovirus 71 replication by regulating IRES-dependent translation of viral proteins. *Antiviral Res.* **2014**, *106*, 80–85. [[CrossRef](#)]
462. Welsbie, D.S.; Ziogas, N.K.; Xu, L.; Kim, B.J.; Ge, Y.; Patel, A.K.; Ryu, J.; Lehar, M.; Alexandris, A.S.; Stewart, N.; et al. Targeted disruption of dual leucine zipper kinase and leucine zipper kinase promotes neuronal survival in a model of diffuse traumatic brain injury. *Mol. Neurodegener.* **2019**, *14*, 44. [[CrossRef](#)]
463. Benini, R.; Roth, R.; Khoja, Z.; Avoli, M.; Wintermark, P. Does angiogenesis play a role in the establishment of mesial temporal lobe epilepsy? *Int. J. Dev. Neurosci.* **2016**, *49*, 31–36. [[CrossRef](#)]
464. Lee, J.C.; Kim, H.Y.; Lee, S.; Shin, J.; Kim, H.V.; Kim, K.; Baek, S.; Lee, D.; Jeon, H.; Kim, D.; et al. Discovery of Chemicals to Either Clear or Indicate Amyloid Aggregates by Targeting Memory-Impairing Anti-Parallel A $\beta$  Dimers. *Angew. Chem. Int. Ed. Engl.* **2020**, *59*, 11491–11500. [[CrossRef](#)]
465. Grammas, P.; Martinez, J.; Sanchez, A.; Yin, X.; Riley, J.; Gay, D.; Desobry, K.; Tripathy, D.; Luo, J.; Evola, M.; et al. A new paradigm for the treatment of Alzheimer's disease: Targeting vascular activation. *J. Alzheimer's Dis.* **2014**, *40*, 619–630. [[CrossRef](#)]
466. Son, S.M.; Jung, E.S.; Shin, H.J.; Byun, J.; Mook-Jung, I. A $\beta$ -induced formation of autophagosomes is mediated by RAGE-CaMKK $\beta$ -AMPK signaling. *Neurobiol. Aging* **2012**, *33*, 1006.e11–1006.e23. [[CrossRef](#)]
467. Wrasidlo, W.; Crews, L.A.; Tsigelny, I.F.; Stocking, E.; Kouznetsova, V.L.; Price, D.; Paulino, A.; Gonzales, T.; Overk, C.R.; Patrick, C.; et al. Neuroprotective effects of the anti-cancer drug sunitinib in models of HIV neurotoxicity suggests potential for the treatment of neurodegenerative disorders. *Br. J. Pharmacol.* **2014**, *171*, 5757–5773. [[CrossRef](#)]
468. Fields, J.A.; Metcalf, J.; Overk, C.; Adame, A.; Spencer, B.; Wrasidlo, W.; Florio, J.; Rockenstein, E.; He, J.J.; Masliah, E. The anticancer drug sunitinib promotes autophagy and protects from neurotoxicity in an HIV-1 Tat model of neurodegeneration. *J. Neurovirol.* **2017**, *23*, 290–303. [[CrossRef](#)]

469. Pu, S.Y.; Xiao, F.; Schor, S.; Bekerman, E.; Zanini, F.; Barouch-Bentov, R.; Nagamine, C.M.; Einav, S. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment. *Antiviral Res.* **2018**, *155*, 67–75. [[CrossRef](#)]
470. Luo, J.; Zhang, Y.; Wang, Y.; Liu, Q.; Chen, L.; Zhang, B.; Luo, Y.; Huang, S.; Guo, X. Rhabdovirus Infection Is Dependent on Serine/Threonine Kinase AP2-Associated Kinase 1. *Life* **2020**, *10*, 170. [[CrossRef](#)]
471. Siracusa, R.; Paterniti, I.; Cordaro, M.; Crupi, R.; Bruschetta, G.; Campolo, M.; Cuzzocrea, S.; Esposito, E. Neuroprotective Effects of Temsirolimus in Animal Models of Parkinson's Disease. *Mol. Neurobiol.* **2018**, *55*, 2403–2419. [[CrossRef](#)]
472. Decressac, M.; Björklund, A. mTOR inhibition alleviates L-DOPA-induced dyskinesia in parkinsonian rats. *J. Parkinson's Dis.* **2013**, *3*, 13–17. [[CrossRef](#)]
473. Jiang, T.; Yu, J.T.; Zhu, X.C.; Zhang, Q.Q.; Cao, L.; Wang, H.F.; Tan, M.S.; Gao, Q.; Qin, H.; Zhang, Y.D.; et al. Temsirolimus attenuates tauopathy in vitro and in vivo by targeting tau hyperphosphorylation and autophagic clearance. *Neuropharmacology* **2014**, *85*, 121–130. [[CrossRef](#)] [[PubMed](#)]
474. Frederick, C.; Ando, K.; Leroy, K.; Héraud, C.; Suain, V.; Buée, L.; Brion, J.P. Rapamycin ester analog CCI-779/Temsirolimus alleviates tau pathology and improves motor deficit in mutant tau transgenic mice. *J. Alzheimer's Dis.* **2015**, *44*, 1145–1156. [[CrossRef](#)] [[PubMed](#)]
475. Jiang, T.; Yu, J.T.; Zhu, X.C.; Tan, M.S.; Wang, H.F.; Cao, L.; Zhang, Q.Q.; Shi, J.Q.; Gao, L.; Qin, H.; et al. Temsirolimus promotes autophagic clearance of amyloid- $\beta$  and provides protective effects in cellular and animal models of Alzheimer's disease. *Pharmacol. Res.* **2014**, *81*, 54–63. [[CrossRef](#)] [[PubMed](#)]
476. Menzies, F.M.; Huebener, J.; Renna, M.; Bonin, M.; Riess, O.; Rubinsztein, D.C. Autophagy induction reduces mutant ataxin-3 levels and toxicity in a mouse model of spinocerebellar ataxia type 3. *Brain* **2010**, *133*, 93–104. [[CrossRef](#)]
477. Saravia, R.; Flores, Á.; Plaza-Zabala, A.; Busquets-Garcia, A.; Pastor, A.; de la Torre, R.; Di Marzo, V.; Marsicano, G.; Ozaita, A.; Maldonado, R.; et al. CB(1) Cannabinoid Receptors Mediate Cognitive Deficits and Structural Plasticity Changes During Nicotine Withdrawal. *Biol. Psychiatry* **2017**, *81*, 625–634. [[CrossRef](#)] [[PubMed](#)]
478. Launay, N.; Aguado, C.; Fourcade, S.; Ruiz, M.; Grau, L.; Riera, J.; Guilera, C.; Giròs, M.; Ferrer, I.; Knecht, E.; et al. Autophagy induction halts axonal degeneration in a mouse model of X-adrenoleukodystrophy. *Acta Neuropathol.* **2015**, *129*, 399–415. [[CrossRef](#)]
479. Konoeda, F.; Shichita, T.; Yoshida, H.; Sugiyama, Y.; Muto, G.; Hasegawa, E.; Morita, R.; Suzuki, N.; Yoshimura, A. Therapeutic effect of IL-12/23 and their signaling pathway blockade on brain ischemia model. *Biochem. Biophys. Res. Commun.* **2010**, *402*, 500–506. [[CrossRef](#)]
480. Yang, L.; Liu, Y.; Wang, Y.; Li, J.; Liu, N. Azeliragon ameliorates Alzheimer's disease via the Janus tyrosine kinase and signal transducer and activator of transcription signaling pathway. *Clinics* **2021**, *76*, e2348. [[CrossRef](#)]
481. Zhou, Y.; Leng, X.; Luo, S.; Su, Z.; Luo, X.; Guo, H.; Mo, C.; Zou, Q.; Liu, Y.; Wang, Y. Tolerogenic Dendritic Cells Generated with Tofacitinib Ameliorate Experimental Autoimmune Encephalomyelitis through Modulation of Th17/Treg Balance. *J. Immunol. Res.* **2016**, *2016*, 5021537. [[CrossRef](#)]
482. Günaydin, C.; Önger, M.E.; Avcı, B.; Bozkurt, A.; Terzi, M.; Bilge, S.S. Tofacitinib enhances remyelination and improves myelin integrity in cuprizone-induced mice. *Immunopharmacol. Immunotoxicol.* **2021**, *43*, 790–798. [[CrossRef](#)]
483. Alshammari, A.; Alharbi, M.; Albekairi, N.A.; Albekairi, T.H.; Alharbi, O.O.; Yeapuri, P.; Singh, S. Protective Effect of CP690550 in MPTP-Induced Parkinson's Like Behavioural, Biochemical and Histological Alterations in Mice. *Neurotox. Res.* **2022**, *40*, 564–572. [[CrossRef](#)] [[PubMed](#)]
484. Figueroa-Romero, C.; Monteagudo, A.; Murdock, B.J.; Famie, J.P.; Webber-Davis, I.F.; Piecuch, C.E.; Teener, S.J.; Pacut, C.; Goutman, S.A.; Feldman, E.L. Tofacitinib Suppresses Natural Killer Cells In Vitro and In Vivo: Implications for Amyotrophic Lateral Sclerosis. *Front. Immunol.* **2022**, *13*, 773288. [[CrossRef](#)] [[PubMed](#)]
485. Risner, K.; Ahmed, A.; Bakovic, A.; Kortchak, S.; Bhalla, N.; Narayanan, A. Efficacy of FDA-Approved Anti-Inflammatory Drugs Against Venezuelan Equine Encephalitis Virus Infection. *Viruses* **2019**, *11*, 1151. [[CrossRef](#)] [[PubMed](#)]
486. Huang, Y.; Li, Q.; Tian, H.; Yao, X.; Bakina, O.; Zhang, H.; Lei, T.; Hu, F. MEK inhibitor trametinib attenuates neuroinflammation and cognitive deficits following traumatic brain injury in mice. *Am. J. Transl. Res.* **2020**, *12*, 6351–6365.
487. Christensen, S.T.; Haanes, K.A.; Spray, S.; Grell, A.S.; Warfvinge, K.; Edvinsson, L.; Johansson, S.E. Pre-clinical effects of highly potent MEK1/2 inhibitors on rat cerebral vasculature after organ culture and subarachnoid haemorrhage. *Clin. Sci.* **2019**, *133*, 1797–1811. [[CrossRef](#)] [[PubMed](#)]
488. Park, E.S.; Kim, S.; Huang, S.; Yoo, J.Y.; Körbelin, J.; Lee, T.J.; Kaur, B.; Dash, P.K.; Chen, P.R.; Kim, E. Selective Endothelial Hyperactivation of Oncogenic KRAS Induces Brain Arteriovenous Malformations in Mice. *Ann. Neurol.* **2021**, *89*, 926–941. [[CrossRef](#)]
489. Ballabh, P.; Xu, H.; Hu, F.; Braun, A.; Smith, K.; Rivera, A.; Lou, N.; Ungvari, Z.; Goldman, S.A.; Csiszar, A.; et al. Angiogenic inhibition reduces germinal matrix hemorrhage. *Nat. Med.* **2007**, *13*, 477–485. [[CrossRef](#)]
490. Rezzola, S.; Guerra, J.; Krishna Chandran, A.M.; Loda, A.; Cancarini, A.; Sacristani, P.; Semeraro, F.; Presta, M. VEGF-Independent Activation of Müller Cells by the Vitreous from Proliferative Diabetic Retinopathy Patients. *Int. J. Mol. Sci.* **2021**, *22*, 2179. [[CrossRef](#)]