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## RIPK1 Inhibitors

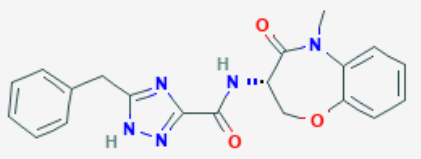
### Evidence Summary

Can reduce cell loss and inflammation in response to inflammatory and oxidative stress by blocking necroptotic cell death. Good safety in Phase 1 trials, but further clinical validation is needed.

**Neuroprotective Benefit:** May protect against neuronal loss to a variety of cell stressors, reduce inflammation, and promote a neuroprotective phenotype in microglia. Clinical validation is needed.

**Aging and related health concerns:** May reduce inflammation-mediated damage and cell loss, stabilize atherosclerotic plaques, and improve insulin sensitivity, but needs to be clinically validated.

**Safety:** Well-tolerated in Phase 1 studies with risk for skin irritation at high doses. Further studies are needed to establish safe and effective dosing.

<b>Availability:</b> Clinical trials	<b>Dose:</b> Not established, twice daily dosing expected based on clinical trials	GSK2982772 <b>Chemical formula:</b> C <sub>20</sub> H <sub>19</sub> N <sub>5</sub> O <sub>3</sub> <b>MW:</b> 377.404 g/mol
<b>Half-life:</b> DNL747 ~12 hours GSK2982772: 2-3 hours + slower terminal phase 5-6 hours	<b>BBB:</b> DNL747 is penetrant	 <p>Source: <a href="#">PubChem</a> Structural information for DNL747 and DNL758 not currently available.</p>
<b>Clinical trials:</b> Phase 1 safety for DNL747 (n=56), GSK2982772 (n=79). Active Phase 2 for Alzheimer's, ALS, rheumatoid arthritis, psoriasis, colitis.	<b>Observational studies:</b> RIPK1 expression elevated in tissue from patients with neurodegenerative and inflammatory diseases	

## What is it?

Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is a multi-domain protein that serves as a mediator for cell death and inflammation. RIPK1 serves as an initiating factor for necroptosis, which is a programmed form of necrosis. Necrotic cell death is associated with the release of damage-associated molecular pattern molecules (DAMPs), which promote inflammation and exacerbate damage to surrounding cells. Necroptosis, then, is a programmed method of inflammatory cell death, whereas apoptosis is a programmed method of non-inflammatory cell death. RIPK1 serves as an integrator of various cell signaling events which can regulate cell responses and determine cell fate [1]. Its activation is regulated by multiple post-translational modifications, especially ubiquitination and phosphorylation. The activation of RIPK1 can trigger the formation of the necrosome, which initiates the inflammatory necroptotic cell death cascade. The execution of necroptosis requires the activation of the downstream mediators RIPK3 and MLKL, such that cells lacking MLKL may undergo a shift in phenotype, but fail to undergo necroptotic cell death in response to RIPK1 activation. RIPK1 is not essential for all forms of necroptotic cell death, but is responsible for the activation of necroptosis downstream from TNF, which is the best studied necroptosis stimulator [2]. Furthermore, RIPK1 mediated necroptosis is inhibited in the presence of caspase activity, particularly caspase-8, which instead drives a cell toward apoptotic cell death.



RIPK1 kinase inhibitors have been tested in a variety of animal models for inflammatory and neurodegenerative diseases, however, the early compounds based off a molecule called Necrostatin-1 have poor drug properties [3]. Next generation RIPK1 kinase inhibitors have been developed and showed good safety in pilot Phase 1 studies. DNL747 is being developed by Denali Therapeutics for Alzheimer's disease and ALS, DNL758 is being developed by Denali and GSK2982772 is being developed by GlaxoSmithKline for peripheral inflammatory diseases, including rheumatoid arthritis, psoriasis, and ulcerative colitis.

**Neuroprotective Benefit:** May protect against neuronal loss to a variety of cell stressors, reduce inflammation, and promote a neuroprotective phenotype in microglia. Clinical validation is needed.

*Types of evidence:*

- 6 observational studies for RIPK1 expression in postmortem tissue for AD, VD, ALS, MS
- Numerous laboratory studies (for Necrostatin series RIPK1 inhibitors)

*Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?*

There is currently no evidence to indicate whether RIPK1 inhibitors are neuroprotective in humans, however, RIPK1 activation is implicated in neurodegeneration based on studies in human postmortem tissue. Clinical trials have recently been initiated for the blood brain barrier (BBB) penetrant RIPK1 inhibitor, DNL747, for Alzheimer's disease (AD) ([NCT03757325](#)) and Amyotrophic lateral sclerosis (ALS) ([NCT03757351](#)).

RIPK1 can act as a transcriptional regulator, and RIPK1 regulated genes are highly enriched in the transcriptomic profile of genes altered in AD [4], and other neurodegenerative diseases [5]. A transcriptomic microarray analysis found that the mRNA for the endogenous RIPK1 inhibitor Tak1 decreases in the brain with age [6]. Brain Tak1 mRNA was decreased 1.33-fold in people over age 60 compared to the those under age 40, and the protein level was also reduced in the aged brain prefrontal cortex. This loss of inhibition suggests that the aged brain is more sensitive to RIPK1 activating stimuli, such as TNF $\alpha$ .

Activation of RIPK1 in microglia is associated with pro-inflammatory cytokine production, while activation of RIPK1 in neurons and oligodendrocytes is associated with cell death. The different responses stem from differential expression of the downstream mediators of the necroptosis cell death signaling cascade, RIPK3 and MLKL. Levels of activated RIPK1, based on S166 phosphorylation, have

been found to be increased in the microglia of AD patients, indicative of elevated damage-inducing inflammation [5]. In the AD brain RIPK1 colocalizes with RIPK3 and MLKL in neurons with high levels of phosphorylated tau and the levels correlate with Braak stage [4]. RIPK1 levels are also inversely correlated with brain weight ( $R=-0.333$ ;  $P=1.1 \times 10^{-3}$ ) and cognitive scores based on the Mini Mental State Examination (MMSE). This suggests that RIPK1 mediated necroptosis may contribute to neuronal loss in AD.

In a comparative histological study, the hippocampus from an individual with vascular dementia had higher levels of inflammatory cytokines associated with RIPK1 activation, including  $\text{TNF}\alpha$ , as well as evidence of both apoptotic and necrotic cells [7]. In contrast, the hippocampus from the individual without dementia showed some apoptotic cells, but no necrotic cells, suggesting that high inflammation may activate necroptotic cell loss and contribute to the development of cognitive impairment.

Caution is warranted in interpreting the contribution of necroptosis mediated cell loss in neurodegenerative diseases based on postmortem tissue because hypoxia can induce RIPK1, and many genes involved in cell death are upregulated during the early postmortem period [8]. However, the localization of elevated RIPK1 specifically in areas with prominent disease-associated pathology suggest that the increase in RIPK1 is disease relevant.

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Elevated levels of RIPK1 in the CNS are associated with microglial mediated inflammation, axon degeneration, and necrotic cell death.

#### **Alzheimer's disease: Potential benefit (preclinical)**

Inhibition of the kinase activity of RIPK1 has been shown to be neuroprotective in several rodent models of AD. Treatment with the RIPK1 kinase inhibitor Necrostatin-1s has been shown to reduce  $\text{A}\beta$  plaque burden, tau aggregation, and levels of pro-inflammatory cytokines, as well as improve performance on spatial memory tests in APP/PS1 mice [4; 5; 9], and reduce cell loss in the 5XFAD mouse model [4].

RIPK1 is an attractive target for AD because it serves as a mediator of cellular toxicity that is downstream of a variety of cell stressors and processes that are dysregulated in the context of AD,



which is advantageous in a patient population where the underlying disease etiology is heterogeneous. Examples of stressors that induce RIPK1 include disruption of cholesterol homeostasis, excitotoxicity, and dysregulated mRNA processing [10; 11; 12]. Inhibition of RIPK1 kinase activity has been shown to protect against the loss of cell viability in response to these stressors in preclinical models, due to its role in regulating neuronal cell death [2]. RIPK1 also plays a critical role in driving axon degeneration independent of apoptosis and its inhibition has been shown to prevent subsequent mitochondrial fragmentation and loss of axon function following injury in culture and animal models [11; 13].

RIPK1 can also promote neurological damage by promoting a pro-inflammatory environment and driving microglia toward a disease-associated phenotype [5]. Disease-associated microglia are thought to be derived from the population of homeostatic microglia by acquiring a unique transcriptional profile. Since RIPK1 regulates many of the genes associated with the disease-associated microglia profile, its activation in response to chronic cell stress is hypothesized to be one of major drivers of this pathogenic cell population. In mice, RIPK1 activation can lead to an impairment of lysosomal function in microglia, while RIPK1 inhibition can promote effective microglial clearance of A $\beta$  [5].

Therefore, RIPK1 inhibition may protect against microglial dysfunction, the exacerbation of inflammation, and neuronal loss induced by a wide variety of cell stressors.

### **Amyotrophic Lateral Sclerosis: Potential benefit (preclinical)**

The dysregulation of RIPK1 is implicated in the pathogenesis of ALS based on the interaction between RIPK1 with several genes associated with ALS. Loss of function mutations in the ubiquitin binding protein optineurin sensitize cells to TNF $\alpha$  induced inflammation and necroptosis, which stems from the activation of RIPK1 in microglia and oligodendrocytes, respectively [14]. The partial loss of TKB1, an endogenous inhibitor of RIPK1, is a major genetic cause of combined ALS/FTD [6]. The expression of necroptotic mediators, including RIPK1, has also been found to be elevated in the spinal cord of the SOD<sup>G93A</sup> mouse model [14]. Cell death could be reduced, and behavioral deficits delayed in these genetic ALS mouse models when RIPK1 kinase activity was inhibited using Necrostatin-1 or transgenic models.

In cell culture, astrocytes from ALS patients were shown to secrete a soluble factor that could promote RIPK1 dependent necroptosis in co-cultured neurons [15]. It is still unclear, however, how much RIPK1 activity contributes to disease progression in ALS patients, and whether it is a primary driver of motor neuron loss. One study examining postmortem tissue from the primary motor cortex of ALS patients found no change in RIPK1 expression [8], while a separate study found it was increased in the spinal

cord in areas of demyelination [14]. The discrepancy may be related to a role for pathogenic RIPK1 activation only in certain cell types, and/or a localization specifically to regions of white matter damage, which has also been reported in multiple sclerosis [16].

### Parkinson's disease: Potential benefit (preclinical)

Several genes associated with Parkinson's disease are involved in mitochondrial homeostasis, leading to dysregulated mitophagy, mitochondrial fragmentation, and excessive reactive oxygen species (ROS) production. Preclinical models suggest that RIPK1 acts as a sensor for ROS and is activated in response to oxidative stress, which then triggers neuronal cell death [17]. The RIPK1 kinase inhibitor Necrostatin-1 has been shown to protect against the loss of dopaminergic cell viability in response to a deficiency in the mitochondria protein Opa1, or the neurotoxins 6-OHDA and MPTP [18; 19]. While RIPK1 inhibition does not correct the underlying driver of mitochondrial dysfunction, it can mitigate downstream cell loss, and thus may slow disease progression.

### Ischemic brain injury: Potential benefit (preclinical)

RIPK1 dependent necroptosis is the dominant driver of cell loss in the context of ischemic brain injury, such as stroke or intracerebral hemorrhage [20]. RIPK1 kinase inhibitors have been shown to be neuroprotective in a variety of rodent models of ischemic brain injury by blocking necroptotic cell death [2].

APOE4 interactions: Unknown

**Aging and related health concerns:** May reduce inflammation-mediated damage and cell loss, stabilize atherosclerotic plaques, and improve insulin sensitivity, but needs to be clinically validated.

*Types of evidence:*

- 3 observational studies for RIPK1 expression in atherosclerotic tissue, tumors, adipose tissue
- Several laboratory studies (for Necrostatin series RIPK1 inhibitors)

### Atherosclerosis: Potential benefit (preclinical)

Necroptosis has been found to be activated in advanced carotid plaque samples from the Biobank of Karolinska Endarterectomy (BiKE) based on expression of phosphorylated MLKL, which is the downstream effector of necroptosis [21]. Expression of necroptosis mediators RIPK1, RIPK3, and MLKL is upregulated in vascular endothelial cells in the presence of atherogenic oxidized LDL (oxLDL) [21; 22].



The induction of these necroptotic factors may stem from the oxLDL mediated upregulation of vascular peroxidase 1 (VPO1) and the activation of  $\beta$ -catenin signaling. In hyperlipidemic patients, the plasma level of necroptotic mediators, including RIPK1, is positively correlated with VPO1 ( $R=0.8710$ ) [22].

Treatment of atherosclerotic (ApoE<sup>-/-</sup>) mice with the RIPK1 kinase inhibitor Necrostatin-1 reduced the size of established lesions by 27% and reduced overall lesion burden by 68% [21]. Lesion size was similarly reduced through the use of RIP1 antisense oligonucleotides [23]. Necroptotic macrophages also play a key role in the pathogenesis of atherosclerosis as a source of proinflammatory cytokines and DAMPs which promote plaque inflammation and instability. This inflammatory response can be significantly attenuated by the knockdown of RIP1 in macrophages [23], suggesting that RIPK1 inhibitors may protect against atherosclerosis-associated adverse events by targeting a key driver of plaque formation and instability.

### **Diabetes: Potential benefit (preclinical)**

A genetic SNP analysis in the METSIM cohort of over 1800 people identified 5 SNPs in linkage disequilibrium with RIP1 that were associated with a 75-89% increased risk for diabetes (adjusted odds ratios OR: 1.75–1.89;  $P<10^{-5}$ ) [23]. Individuals with the risk allele also had increased expression of RIP1 in adipose tissue.

The activation of cell death pathways is influenced by metabolic condition, and hyperglycemia can promote a shift from apoptosis to RIPK1 dependent necroptosis [24]. The core mediators of necroptosis, RIPK1, RIPK3, and MLKL have been found to be increased in the liver and adipose tissue of obese (ob/ob, high-fat diet) and type 2 diabetic (db/db) mouse models [25]. Inhibition of these factors using transgenic knockout lines or with the RIPK1 kinase inhibitor Necrostatin-1 improved insulin sensitivity and glucose tolerance in these mice by regulating insulin signaling. RIP1 antisense oligonucleotides could also improve insulin resistance, and decrease fat mass (by 50-65%) in obese mice [23]. This suggests that RIPK1 inhibitors may improve glucometabolism.

### **Inflammation: Potential benefit**

RIPK1 is associated with both necrosis-associated inflammation and cell death independent inflammation. RIPK1 kinase activity plays a primary role in the initiation of multiple mechanisms of inflammatory cell death in response to activation of the TNFR1 receptor by TNF $\alpha$ . RIPK1 also plays a role in ER-stress induced activation of the inflammasome through induction of ROS production and mitochondrial dysfunction [26]. Therefore, RIPK1 is an attractive target for diseases associated with high levels of TNF $\alpha$  mediated inflammation. RIPK1 kinase inhibitors have been shown to reduce



inflammation and cell loss in animal models of inflammatory autoimmune diseases [1; 16; 27]. Two are currently under clinical development for chronic inflammatory conditions including GSK2982772 for rheumatoid arthritis, ulcerative colitis, and plaque psoriasis, and DNL758 for rheumatoid arthritis and psoriasis.

#### **Liver disease: Potential benefit (rodent model)**

RIPK1 is involved in liver homeostasis, and inhibition of RIPK1 kinase activity has been shown to protect against hepatotoxicity in rodents. In a model of acetaminophen induced acute liver failure, pretreatment with the RIPK1 kinase inhibitor Necrostatin-1 decreased the production of pro-inflammatory cytokines and ROS, and protected against hepatocyte cell loss [28]. Therefore, the use of RIPK1 inhibitors may protect the liver by conferring resistance to cellular stressors.

#### **Cancer: Potential benefit or harm depending on tumor type (preclinical)**

The activation of necroptosis has been proposed as a possible mechanism to promote tumor cell death via necrosis in the context of resistance to chemotherapeutic agents, which primarily promote tumor cell death via apoptosis. However, there is evidence to suggest that RIPK signaling may play different roles in different tumor types based on the tissue type and tumor microenvironment. Necroptotic mediator (RIPK1, RIPK3, or MLKL) expression has been found to be low or absent in a variety of cancer cell lines, such as breast cancer, colorectal cancer, leukemia, ovarian cancer, and melanoma, which is associated with worse prognosis for these types of cancer [29]. Meanwhile, RIPK1 expression is upregulated in other types of cancer, such as glioblastoma, lung cancer, and pancreatic cancer, where RIPK1 signaling is oncogenic.

**Safety:** Well-tolerated in Phase 1 studies with risk for skin irritation at high doses. Further studies are needed to establish safe and effective dosing.

#### *Types of evidence:*

- 2 Phase 1 clinical trials in healthy volunteers (DNL747 n=56; GSK2982772 n=79)
- Numerous laboratory studies (primarily for Necrostatins, 2 GLP toxicology studies for DNL747)

Attempts to target apoptotic cell death through the use of caspase inhibitors for inflammatory diseases have been hindered by safety concerns, such as the compensatory induction of necrotic cell death stemming from the induction of RIPK1 mediated necroptosis in the absence of Caspase-8 [2; 30]. Targeting necroptosis is expected to be a safer alternative since, unlike apoptosis, it generally plays



very little role in homeostatic mechanisms in healthy tissue. The genes associated with necroptosis are only found in higher order organisms, and necroptosis is thought to have evolved as a mechanism to abort defective embryos [1]. Therefore, necroptosis appears to be a developmental program that gets reactivated under pathological conditions involving excessive levels of cell stress.

Of the major necroptotic factors, RIPK1 is expected to be the best drug target with respect to both safety and efficacy for inflammatory and neurodegenerative diseases. Loss of MLKL shows less protection in animal models, while inhibition of RIPK3 can trigger apoptosis in some cases [1]. Necroptosis is activated in response to some viral pathogens which is driven by TLR activation of RIPK3, thus targeting only RIPK1 preserves this host defense mechanism [2]. Although RIPK1 activation can play different roles in different cell types depending on the presence or absence of interacting signaling partners, its primary role is in promoting necroptotic cell death and inflammation [31]. Furthermore, RIPK1 inhibitors are also thought to be a safer alternative to TNF $\alpha$  inhibitors for CNS indications because TNFR2 is important for neural regeneration and RIPK1 selectively affects TNF $\alpha$  mediated processes downstream from the TNF $\alpha$ -TNFR1 interaction [2].

Inhibition of RIPK1 kinase activity through transgenic models or small molecules, such as the Necrostatin compounds, have been effective in a variety of animal models, and no major safety concerns have been noted in these studies. However, the Necrostatins are not amenable for clinical development due to their low metabolic stability [3].

The good safety profile for RIPK1 inhibitors is due, in part, to their high degree of specificity and selectivity, which is highly unusual for kinase inhibitors, since they tend to target multiple classes of kinases. The selectivity of these allosteric small molecule RIPK1 inhibitors stems from the kinase structure of RIPK1 due to the unusual flexibility of its allosteric back pocket [31].

Two RIPK1 kinase inhibitors have been tested in Phase 1 RCTs thus far.

DNL747 is a brain penetrant RIPK1 inhibitor that was tested in a double-blind, placebo controlled RCT in healthy volunteers (n=56) for safety, tolerability, pharmacokinetics, and pharmacodynamics ([Press release](#)). It was found to be well tolerated in 28-day GLP studies at a dose up to 500 mg/kg in rats, and up to 100 mg/kg in cynomolgus monkeys ([SEC filing](#)). Cutaneous lesions due to lymphocytic infiltration of the skin and lymphoid hyperplasia of the spleen and lymph nodes were detected in monkeys at the highest tested dose of 500 mg/kg. Preclinical modeling predicts that the half-life is compatible with twice daily dosing. The majority (92%) of adverse events were mild and there was no clear dose relationship with adverse events ([Clinical presentation Denali R&D Day 12/10/18](#)). The most common

adverse events that were not related to the medical devices used for assessments were nausea (14%) and fatigue (10%). The terminal plasma half-life was 12 hours across doses, and the unbound CSF: plasma ratio was  $1.51 \pm 0.23$ . All tested doses showed >90% RIPK1 inhibition in the blood based on an assay of pS166 inhibition that is maintained with twice daily dosing. CSF inflammatory cytokine levels were not significantly affected, as they were not elevated in the healthy subjects.

GSK2982772 is a RIPK1 inhibitor that binds to the back allosteric pocket of RIPK1 and was tested in a Phase 1 double-blind, placebo controlled RCT in healthy male volunteers aged 18-65 (n=79) for safety, tolerability, pharmacokinetics, and pharmacodynamics ([NCT02302404](#)). It was tested in a single ascending dose study up to 120 mg and in a multiple ascending dose from 20 mg once daily up to 120 mg twice daily [32]. The  $C_{max}$  of the drug was 1 hour and the half-life ( $T_{1/2}$ ) was 2-3 hours, with no evidence of drug accumulation with multiple dosing. The drug showed dose-dependent target engagement based on an immunoassay specific for RIPK1 and the inhibition of MIP-1 $\alpha$  and MIP-1 $\beta$ . The adverse events were mild, and the drug was generally well-tolerated. The most common adverse events were dermatitis and headache, with the risk for contact dermatitis being found as drug related.

#### Sources and dosing:

DNL747 and DNL758 are being developed by Denali Therapeutics for neurodegenerative diseases and peripheral inflammatory diseases, respectively, due to their difference in BBB permeability. The RIPK1 inhibitor program at Denali is based on the work of Junying Yuan at Harvard Medical School. DNL747 has been clinically tested in an oral formulation with twice daily dosing. The dose range tested has not been disclosed. It is currently being tested in clinical trials.

GSK2982772 is being developed by GlaxoSmithKline for peripheral inflammatory diseases and was tested in both capsule and tablet oral formulations at doses up to 120 mg BID. Twice daily dosing is considered optimal based on its pharmacokinetic profile. It is currently being tested in clinical trials, but is available for research use from commercial suppliers.

#### Research underway:

Denali Therapeutics has partnered with Sanofi for the development of DNL747 (SAR-443060) for neurological diseases, with Sanofi funding clinical development in MS and ALS, and Denali funding development for AD ([Press Release](#)). Sanofi will also fund the clinical development of DNL758 for peripheral inflammatory diseases.

There are currently two active clinical trials for DNL747. There are Phase 1 trials testing safety, tolerability PK and PD in AD patients ([NCT03757325](#)), and ALS patients ([NCT03757351](#)). Both trials have estimated completion dates of August 2019.

There are two active clinical trials for GSK2982772. There is a Phase 1 study examining the pharmacokinetics of a modified release coated tablet formulation ([NCT03649412](#)), and a Phase 2 study in ulcerative colitis ([NCT02903966](#)). According to [Clinicaltrials.gov](#), Phase 2 trials have also been completed in patients with psoriasis ([NCT02776033](#)) and rheumatoid arthritis ([NCT02858492](#)) in 2018, however, results have not yet been disclosed.

There are medicinal chemistry efforts underway to develop novel RIPK1 inhibitors that have better pharmacokinetic properties. Junying Yuan, Gregory D. Cuny and Alexei Degterev, who are co-founders of Incro Pharmaceuticals, which is a subsidiary of Denali, have developed compounds that are hybrids of ponatinib and Necrostatin-1. Their lead compound, PN10 was shown to be highly specific for RIPK1 and had 20-fold greater inhibitory activity relative to Necrostatin-1 [33]. Scientists at Genentech have been developing and optimizing RIPK1 kinase inhibitors using a metabolically stable pentafluoroethyl group as opposed to a lipophilic aromatic group. Their lead compound 29 was found to have 63% oral bioavailability in rats [34]. The scientists at Takeda are also using medicinal chemistry to optimize the pharmacokinetic properties of RIPK1 inhibitors. Their lead compound 22 is orally bioavailable, brain penetrant, and protective in the EAE neuroinflammatory mouse model [35]. It is not known whether any of these compounds will be pursued for further clinical development.

#### Search terms:

Pubmed, Google: RIPK1, DNL747, DNL758, GSK2982772

- Alzheimer's, Parkinson's, ALS, neurodegeneration, inflammation, aging, diabetes, cardiovascular, cancer, necroptosis, safety, clinical trials

Websites visited for RIPK inhibitors:

- Clinicaltrials.gov [DNL747](#), [GSK2982772](#)
- PubChem [GSK2982772](#)

#### References:

1. Shan B, Pan H, Najafov A et al. (2018) Necroptosis in development and diseases. *Genes Dev* 32, 327-340. <https://www.ncbi.nlm.nih.gov/pubmed/29593066>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5900707/>

2. Degterev A, Ofengeim D, Yuan J (2019) Targeting RIPK1 for the treatment of human diseases. *Proceedings of the National Academy of Sciences* 116, 9714-9722. <https://www.pnas.org/content/pnas/116/20/9714.full.pdf>
3. Oliveira SR, Amaral JD, Rodrigues CMP (2018) Mechanism and disease implications of necroptosis and neuronal inflammation. *Cell Death Dis* 9, 903-903. <https://www.ncbi.nlm.nih.gov/pubmed/30185777>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6125291/>
4. Caccamo A, Branca C, Piras IS *et al.* (2017) Necroptosis activation in Alzheimer's disease. *Nature Neuroscience* 20, 1236. <https://doi.org/10.1038/nn.4608>
5. Ofengeim D, Mazzitelli S, Ito Y *et al.* (2017) RIPK1 mediates a disease-associated microglial response in Alzheimer's disease. *Proc Natl Acad Sci U S A* 114, E8788-E8797. <https://www.ncbi.nlm.nih.gov/pubmed/28904096>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642727/>
6. Xu D, Jin T, Zhu H *et al.* (2018) TBK1 Suppresses RIPK1-Driven Apoptosis and Inflammation during Development and in Aging. *Cell* 174, 1477-1491. <http://www.sciencedirect.com/science/article/pii/S0092867418309693>
7. Belkhef M, Beder N, Mouhoub D *et al.* (2018) The involvement of neuroinflammation and necroptosis in the hippocampus during vascular dementia. *Journal of Neuroimmunology* 320, 48-57. <http://www.sciencedirect.com/science/article/pii/S0165572818300316>
8. Dermentzaki G, Politi KA, Lu L *et al.* (2019) Deletion of Ripk3 Prevents Motor Neuron Death In Vitro but not In Vivo. *eNeuro* 6, ENEURO.0308-0318.2018. <https://www.ncbi.nlm.nih.gov/pubmed/30815534>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6391588/>
9. Yang S-H, Lee DK, Shin J *et al.* (2017) Nec-1 alleviates cognitive impairment with reduction of A $\beta$  and tau abnormalities in APP/PS1 mice. *EMBO Mol Med* 9, 61-77. <https://www.ncbi.nlm.nih.gov/pubmed/27861127>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5210088/>
10. Takabe W, Urano Y, Vo D-KH *et al.* (2016) Esterification of 24S-OHC induces formation of atypical lipid droplet-like structures, leading to neuronal cell death. *J Lipid Res* 57, 2005-2014. <https://www.ncbi.nlm.nih.gov/pubmed/27647838>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5087868/>
11. Hernández DE, Salvadores NA, Moya-Alvarado G *et al.* (2018) Axonal degeneration induced by glutamate excitotoxicity is mediated by necroptosis. *Journal of Cell Science* 131, jcs214684. <http://jcs.biologists.org/content/joces/131/22/jcs214684.full.pdf>
12. Cheng Z, Shang Y, Gao S *et al.* (2017) Overexpression of U1 snRNA induces decrease of U1 spliceosome function associated with Alzheimer's disease. *Journal of Neurogenetics* 31, 337-343. <https://doi.org/10.1080/01677063.2017.1395425>
13. Arrázola MS, Saquel C, Catalán RJ *et al.* (2019) Axonal Degeneration Is Mediated by Necroptosis Activation. *The Journal of Neuroscience* 39, 3832-3844. <http://www.jneurosci.org/content/jneuro/39/20/3832.full.pdf>
14. Ito Y, Ofengeim D, Najafv A *et al.* (2016) RIPK1 mediates axonal degeneration by promoting inflammation and necroptosis in ALS. *Science* 353, 603-608. <https://www.ncbi.nlm.nih.gov/pubmed/27493188>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5444917/>
15. Re DB, Le Verche V, Yu C *et al.* (2014) Necroptosis drives motor neuron death in models of both sporadic and familial ALS. *Neuron* 81, 1001-1008. <https://www.ncbi.nlm.nih.gov/pubmed/24508385>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951532/>

16. Ofengeim D, Ito Y, Najafov A *et al.* (2015) Activation of necroptosis in multiple sclerosis. *Cell Rep* 10, 1836-1849. <https://www.ncbi.nlm.nih.gov/pubmed/25801023>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494996/>
17. Zhang Y, Su SS, Zhao S *et al.* (2017) RIP1 autophosphorylation is promoted by mitochondrial ROS and is essential for RIP3 recruitment into necrosome. *Nature Communications* 8, 14329. <https://doi.org/10.1038/ncomms14329>
18. Iannielli A, Bido S, Folladori L *et al.* (2018) Pharmacological Inhibition of Necroptosis Protects from Dopaminergic Neuronal Cell Death in Parkinson's Disease Models. *Cell Rep* 22, 2066-2079. <https://www.ncbi.nlm.nih.gov/pubmed/29466734>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5842028/>
19. Wu J-R, Wang J, Zhou S-K *et al.* (2015) Necrostatin-1 protection of dopaminergic neurons. *Neural Regen Res* 10, 1120-1124. <https://www.ncbi.nlm.nih.gov/pubmed/26330837>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4541245/>
20. Linkermann A, Bräsen JH, Darding M *et al.* (2013) Two independent pathways of regulated necrosis mediate ischemia-reperfusion injury. *Proceedings of the National Academy of Sciences* 110, 12024-12029. <https://www.pnas.org/content/pnas/110/29/12024.full.pdf>
21. Karunakaran D, Geoffrion M, Wei L *et al.* (2016) Targeting macrophage necroptosis for therapeutic and diagnostic interventions in atherosclerosis. *Sci Adv* 2, e1600224-e1600224. <https://www.ncbi.nlm.nih.gov/pubmed/27532042>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4985228/>
22. Zhang Y-Z, Wang L, Zhang J-J *et al.* (2018) Vascular peroxide 1 promotes ox-LDL-induced programmed necrosis in endothelial cells through a mechanism involving  $\beta$ -catenin signaling. *Atherosclerosis* 274, 128-138. <http://www.sciencedirect.com/science/article/pii/S0021915018302168>
23. Karunakaran D, Nguyen MA, Geoffrion M *et al.* (2018) Therapeutic inhibition of RIP1 improves metabolic dysfunction and inhibits atherosclerosis in mouse models of cardiometabolic diseases. *The FASEB Journal* 32, 38.31-38.31. [https://www.fasebj.org/doi/abs/10.1096/fasebj.2018.32.1\\_supplement.38.1](https://www.fasebj.org/doi/abs/10.1096/fasebj.2018.32.1_supplement.38.1)
24. McCaig WD, Patel PS, Sosunov SA *et al.* (2018) Hyperglycemia potentiates a shift from apoptosis to RIP1-dependent necroptosis. *Cell Death Discov* 4, 55-55. <https://www.ncbi.nlm.nih.gov/pubmed/29760953>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5945624/>
25. Xu H, Du X, Liu G *et al.* (2019) The pseudokinase MLKL regulates hepatic insulin sensitivity independently of inflammation. *Mol Metab* 23, 14-23. <https://www.ncbi.nlm.nih.gov/pubmed/30837196>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6480316/>
26. Tao L, Lin H, Wen J *et al.* (2018) The kinase receptor-interacting protein 1 is required for inflammasome activation induced by endoplasmic reticulum stress. *Cell Death Dis* 9, 641-641. <https://www.ncbi.nlm.nih.gov/pubmed/29844315>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5974395/>
27. Jhun J, Lee SH, Kim S-Y *et al.* (2019) RIPK1 inhibition attenuates experimental autoimmune arthritis via suppression of osteoclastogenesis. *J Transl Med* 17, 84-84. <https://www.ncbi.nlm.nih.gov/pubmed/30876479>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419814/>
28. Takemoto K, Hatano E, Iwaisako K *et al.* (2014) Necrostatin-1 protects against reactive oxygen species (ROS)-induced hepatotoxicity in acetaminophen-induced acute liver failure. *FEBS Open Bio* 4, 777-787. <https://www.ncbi.nlm.nih.gov/pubmed/25349782> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4208088/>

29. Gong Y, Fan Z, Luo G *et al.* (2019) The role of necroptosis in cancer biology and therapy. *Mol Cancer* 18, 100-100. <https://www.ncbi.nlm.nih.gov/pubmed/31122251>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6532150/>
30. Howley B, Fearnhead HO (2008) Caspases as therapeutic targets. *J Cell Mol Med* 12, 1502-1516. <https://www.ncbi.nlm.nih.gov/pubmed/18298652>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3918066/>
31. Wegner KW, Saleh D, Degterev A (2017) Complex Pathologic Roles of RIPK1 and RIPK3: Moving Beyond Necroptosis. *Trends Pharmacol Sci* 38, 202-225. <https://www.ncbi.nlm.nih.gov/pubmed/28126382>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5325808/>
32. Weisel K, Scott NE, Tompson DJ *et al.* (2017) Randomized clinical study of safety, pharmacokinetics, and pharmacodynamics of RIPK1 inhibitor GSK2982772 in healthy volunteers. *Pharmacol Res Perspect* 5, e00365. <https://www.ncbi.nlm.nih.gov/pubmed/29226626>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5723699/>
33. Najjar M, Suebsuwong C, Ray SS *et al.* (2015) Structure guided design of potent and selective ponatinib-based hybrid inhibitors for RIPK1. *Cell Rep* 10, 1850-1860. <https://www.ncbi.nlm.nih.gov/pubmed/25801024>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494889/>
34. Hamilton GL, Chen H, Deshmukh G *et al.* (2019) Potent and selective inhibitors of receptor-interacting protein kinase 1 that lack an aromatic back pocket group. *Bioorganic & Medicinal Chemistry Letters* 29, 1497-1501. <http://www.sciencedirect.com/science/article/pii/S0960894X19302239>
35. Yoshikawa M, Saitoh M, Katoh T *et al.* (2018) Discovery of 7-Oxo-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine Derivatives as Potent, Orally Available, and Brain-Penetrating Receptor Interacting Protein 1 (RIP1) Kinase Inhibitors: Analysis of Structure–Kinetic Relationships. *Journal of Medicinal Chemistry* 61, 2384-2409. <https://doi.org/10.1021/acs.jmedchem.7b01647>

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