Ferroptosis and the Phase II Oligodendrocyte Crisis

GPX4, Iron, and the Myelin-Bearing Cell

A Drug-Class Landscape for the Mid-Disease Window of the Spectrum of Collapse

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Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by Claude-Opus-4.6

Abstract

Among the cell types of the adult central nervous system, oligodendrocytes occupy a uniquely precarious metabolic position. They contain more iron per cell than any other CNS lineage, sustain the most lipid-intensive synthetic program in the brain, and operate at the frontier of redox balance every minute of their post-mitotic existence. This combination — abundant catalytic iron, abundant polyunsaturated phospholipid, and a reduced antioxidant reserve relative to neurons — renders them the most ferroptosis-primed cells in the brain. This paper argues that ferroptosis inhibition is the load-bearing drug class for Phase II of the Spectrum of Collapse framework: the mid-disease window in which lysosomal failure, tau propagation, microglial state transition, and oligodendrocyte demyelination convert a chronic Phase I bioenergetic erosion into the cortical pathology that anti-amyloid therapeutics encounter at Phase III. We integrate the consensus ferroptosis biochemistry developed by Stockwell, Dixon, Conrad, and colleagues with brain-iron and ferroptosis-in-AD evidence from Ayton, Bush, and Lei, the oligodendrocyte-vulnerability literature anchored by Hambright, Ran, and Friedmann Angeli, and the disease-associated microglia and complement-pruning frameworks of Schwartz, Stevens, Deczkowska, and Hammond. We then map this mechanistic substrate onto the existing pharmacopoeia: the prototypical lipophilic radical-trapping antioxidants ferrostatin-1 and liproxstatin-1; the orally bioavailable iron chelators deferiprone and deferoxamine; the NRF2 activators dimethyl fumarate and bardoxolone-methyl; the GPX4 axis (selenium, ebselen-class compounds); the FSP1/CoQ10 axis; and vitamin E. We argue that the failure of anti-amyloid therapeutics to address Phase II demyelination is not a failure of execution but a category error: the molecular targets of those drugs lie downstream of the oligodendrocyte ferroptotic crisis, not upstream of it. We acknowledge the entrant gap — the Oskar Fischer Prize corpus does not contain a candidate whose primary mechanism is named ferroptosis, because the prize submissions predate the consolidation of ferroptosis as a recognized program — and treat the gap as a feature of corpus vintage rather than a thesis weakness, while identifying lipid-peroxidation-adjacent entrants whose work touches the substrate. We close with a Phase II clinical-trial design that pairs cerebrospinal F2-isoprostanes, plasma neurofilament light, and quantitative susceptibility-mapping MRI for brain iron with myelin water fraction imaging, in MCI-to-mild-AD patients stratified by basal ganglia and white-matter iron load. The ferroptosis-inhibitor class, though young, has

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decisively the best mechanistic match to the Phase II crisis.

Keywords: ferroptosis, oligodendrocyte, GPX4, lipid peroxidation, iron, ferrostatin-1, liproxstatin-1, deferiprone, dimethyl fumarate, FSP1, NRF2, demyelination, Alzheimer's disease, Phase II, Spectrum of Collapse

1. Introduction: The Iron Cell

The oligodendrocyte is the most iron-rich cell of the central nervous system. Histochemical iron staining, quantitative magnetic resonance imaging, and laser-ablation inductively-coupled-plasma mass spectrometry converge on the same finding: across mammalian species, mature myelinating oligodendrocytes accumulate ferritin- and transferrin-bound iron at concentrations that exceed those of neurons, astrocytes, and microglia by a factor of two to ten (Connor et al., 1990; Todorich et al., 2009). The reason is metabolic. Myelin synthesis is among the most energetically and biochemically demanding processes any post-mitotic cell undertakes. A single mature oligodendrocyte must generate and maintain the lipid envelope for as many as fifty axonal internodes, an undertaking that requires elongation and desaturation of fatty acids, hydroxylation of sphingolipids, and the operation of cholesterol biosynthesis at a pace unmatched in adult tissues. Each of these steps depends on iron — directly, through iron-sulfur cluster enzymes such as the desaturases of the SCD and FADS families, and indirectly, through the iron-dependent oxygenases of the mitochondrial respiratory chain that supply the ATP and reducing equivalents on which lipid synthesis runs.

This metabolic logic — abundant iron in service of abundant lipid — has a thermodynamic shadow. The same iron that catalyzes desaturation reactions in the controlled environment of an enzyme active site will, in the presence of hydrogen peroxide and a polyunsaturated fatty acid (PUFA) substrate, catalyze the Fenton reaction and generate hydroxyl radicals at rates limited only by substrate availability. Oligodendrocyte plasma membranes and the myelin sheaths they elaborate are saturated with PUFA-containing phosphatidylethanolamines and phosphatidylcholines. The myelin lipidome is thus a vast substrate pool for lipid peroxidation, and the iron necessary for myelinogenesis is the catalyst that initiates it. Oligodendrocyte vulnerability to ferroptosis is not an accident of biology; it is the obverse face of the metabolic specialization that defines the cell.

The clinical consequence of this duality is the central thesis of this paper. In Phase I of the Spectrum of Collapse — the silent brainstem erosion of mid-adulthood — ferroptosis is held in check by intact glutathione synthesis, intact selenium-dependent glutathione peroxidase 4 (GPX4) activity, and an FSP1/coenzyme Q10 axis that operates in parallel to recycle membrane radical-trapping antioxidants. In Phase II — the hippocampal bridgehead and the white-matter erosion that accompanies it — these defenses begin to fail. Cysteine availability declines as system xc-minus exchange weakens; selenium-dependent GPX4 activity contracts as broader selenoprotein synthesis stalls; iron mobilization from senescent ferritin pools accelerates; and the oligodendrocyte lipid envelope, the largest and most peroxidation-prone surface in the brain, becomes the limiting substrate of a lipid-peroxidation chain reaction that, once initiated, propagates faster than enzymatic defenses can quench it. This is the Phase II oligodendrocyte crisis. It is the architectural reason that the mid-disease window is dominated by demyelination, white-matter hyperintensities on FLAIR imaging, and the disease-associated microglial response that scrubs the resulting myelin debris from the parenchyma. It is the architectural reason that Phase III — the excitatory/inhibitory cortical collapse — arrives when it does, because the loss of oligodendrocyte support and the chronic microglial activation it provokes accelerate every downstream pathology that the field has historically treated as primary.

The remainder of this paper develops the mechanistic case that ferroptosis inhibition is the drug class whose architecture matches the Phase II crisis and that no other class — not anti-amyloid antibodies, not tau immunotherapies, not generic anti-inflammatories — can stand in its place.

2. Ferroptosis Biochemistry: The Stockwell-Dixon-Conrad Consensus

Ferroptosis was defined as a distinct form of regulated cell death in 2012 by Dixon, Stockwell, and colleagues, who showed that the small-molecule erastin induces a cysteine-deprivation-driven, iron-dependent, lipid-peroxidation-mediated demise that is morphologically, biochemically, and genetically separable from apoptosis, necroptosis, and autophagy-dependent cell death (Dixon et al., 2012). The decade since has transformed ferroptosis from a chemical curiosity into a recognized cellular program with a defined regulatory architecture, a well-characterized inhibitor pharmacology, and a clear role in physiological turnover and in disease (Stockwell, 2022).

2.1 The Central Regulator: GPX4

At the center of the program is glutathione peroxidase 4 (GPX4), the only mammalian enzyme that reduces phospholipid hydroperoxides in situ within membranes. Where the cytosolic glutathione peroxidases (GPX1, GPX3) reduce hydrogen peroxide and small-molecule hydroperoxides in solution, GPX4 alone reaches into the membrane lipid bilayer and reduces lipid hydroperoxides — the very species whose accumulation, autocatalytic propagation, and membrane disruption define ferroptotic execution. GPX4 is selenocysteine-dependent: its catalytic residue is encoded by an in-frame UGA codon decoded as selenocysteine via a SECIS-element-dependent translation mechanism. Selenium availability is therefore an upstream determinant of GPX4 activity, and selenium status modulates ferroptosis sensitivity in cell, animal, and tissue models.

The conditional knockout of GPX4 in mice was the experimental crucible in which ferroptosis biology was forged. Friedmann Angeli and colleagues (2014) showed that inducible whole-body GPX4 deletion produces lethal lipid peroxidation and ferroptotic cell death, and that this lethality is rescued by liproxstatin-1, a lipophilic radical-trapping antioxidant. Subsequent tissue-specific deletions clarified the cell-type-specific consequences. Forebrain-specific GPX4 deletion produces hippocampal neuronal loss with cognitive impairment (Hambright et al., 2017). Critically for the present paper, conditional GPX4 deletion in oligodendrocytes produces a phenotype dominated by demyelination, motor deficits, and oligodendrocyte loss with histological features of ferroptosis (Yoo et al., 2010, with

extension by subsequent groups).

2.2 The Lipid Peroxidation Cascade

The substrate of ferroptosis is the polyunsaturated-fatty-acid (PUFA)-containing phospholipid. Three enzymes set the pace at which the substrate is generated and the hydroperoxide is laid down on the membrane.

Acyl-CoA synthetase long-chain family member 4 (ACSL4) activates PUFAs (notably arachidonic and adrenic acids) by attaching coenzyme A, generating PUFA-CoA species that are the preferred substrate for downstream incorporation into phospholipids. ACSL4 deletion confers ferroptosis resistance in vitro and in vivo, and ACSL4 expression correlates with ferroptosis sensitivity across cell lines (Doll et al., 2017).

Lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates PUFA-CoAs into the sn-2 position of phosphatidylethanolamines, generating the membrane species that are most permissive of peroxidation. The ACSL4-LPCAT3 axis thus determines the membrane PUFA pool size and the per-molecule peroxidation susceptibility.

Lipoxygenase 15 (15-LOX, ALOX15) and to a lesser extent ALOX12 and ALOX5 introduce oxygen onto specific PUFA carbons enzymatically, generating the lipid hydroperoxides that initiate the autocatalytic chain. Once initiated, the chain propagates non-enzymatically: a lipid peroxyl radical abstracts hydrogen from a neighboring PUFA, generating a new lipid radical that combines with molecular oxygen to form a new lipid peroxyl radical, and the process repeats until the membrane is peroxidatively shredded or a radical-trapping antioxidant intercepts the propagation step.

2.3 Iron and Fenton Chemistry

The "ferro" in ferroptosis is not decorative. Iron-dependence is the defining biochemical feature: chelation of labile iron prevents ferroptosis even when GPX4 is inhibited, and iron supplementation accelerates it. Two iron pools matter. The labile iron pool (LIP) — cytosolic Fe(II) bound loosely to glutathione, citrate, and other low-molecular-weight ligands — is the Fenton-reactive species that catalyzes the conversion of hydrogen peroxide to hydroxyl radical, which then abstracts hydrogen from membrane PUFAs. The ferritin-bound pool serves as the storage reservoir that, under conditions of ferritinophagy (NCOA4-mediated autophagic degradation of ferritin), releases iron into the LIP and thus arms the cell for ferroptosis. The transferrin receptor, the divalent metal transporter DMT1, and the iron exporter ferroportin set the long-term iron balance, while NCOA4 sets the short-term mobilization rate. Each of these nodes is a candidate intervention point, and each is differentially druggable.

2.4 Defenses Beyond GPX4: FSP1/CoQ10 and DHODH

GPX4 is not the only line of defense. Ferroptosis suppressor protein 1 (FSP1, also known as AIFM2) reduces ubiquinone (CoQ10) to ubiquinol at the plasma membrane, generating a lipid-soluble radical-trapping antioxidant that operates in parallel with GPX4 (Bersuker et al., 2019; Doll et al., 2019). The FSP1-CoQ10-NAD(P)H axis is a parallel rather than redundant defense: it can be functional when GPX4 is impaired and vice versa. Mitochondrial dihydroorotate dehydrogenase (DHODH) provides an additional, mitochondrially compartmentalized reducing equivalent for CoQ10 (Mao et al., 2021). The pharmacological exploitation of these parallel axes — selenium and selenoprotein-cofactor delivery for GPX4, ubiquinol stabilization and FSP1 activation for the parallel arm — is one of the cleanest design opportunities in the ferroptosis-inhibitor space.

2.5 NRF2 and the Transcriptional Reserve

The transcription factor NFE2L2 (NRF2) coordinates a battery of cytoprotective genes whose products span the ferroptosis defense network: SLC7A11 (the cystine importer that supplies glutathione synthesis), GCLC and GCLM (glutathione synthesis enzymes), GPX4 itself, FTH1 and FTL (ferritin subunits), and the heme-degrading HMOX1. NRF2 activators thus constitute an integrated upstream lever on the entire ferroptosis defense system, distinct from the lipid-trapping or chelating mechanisms of the other drug classes. The clinical leverage of NRF2 in multiple sclerosis (dimethyl fumarate) is the most direct precedent for repurposing this axis to oligodendrocyte protection in Alzheimer's disease.

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3. Oligodendrocyte Vulnerability: Why This Cell, Why This Phase

3.1 The Lipid Substrate

The myelin sheath is the largest concentrated phospholipid surface in the adult mammalian organism. The lipid composition of compact myelin is dominated by cholesterol, galactocerebrosides, sphingomyelin, and phosphatidylethanolamines, with a substantial PUFA content carried in the ethanolamine plasmalogens. Plasmalogens are themselves antioxidant — the vinyl-ether bond at the sn-1 position scavenges radicals — but this protective effect is finite. Once the plasmalogen pool is depleted by chronic oxidative stress, the residual PUFA-containing phospholipids become the substrate for an increasingly catalytic lipid-peroxidation chain. The oligodendrocyte plasma membrane and the myelin sheaths it elaborates are, in this sense, the brain's largest peroxidation target.

3.2 The Iron Substrate

Oligodendrocytes acquire iron during their maturation from oligodendrocyte progenitor cells (OPCs) to myelinating oligodendrocytes. Transferrin receptor (TfR1) expression is upregulated during this transition, and the divalent metal transporter DMT1 contributes to non-transferrin-bound uptake. The cell stores its iron in ferritin, but the pool turns over: NCOA4-mediated ferritinophagy releases iron back into the labile pool whenever lipid synthesis demands it. In aged brain, ferritin iron accumulates beyond the cell's capacity to safely sequester it, and in regions where myelin turnover is high — periventricular white matter, the deep gray nuclei, the fornix — the labile iron pool expands. The QSM literature documents this expansion in vivo: iron accumulation in basal ganglia and selected white-matter tracts is a signature of mid-life and a stronger correlate of cognitive trajectory than amyloid load by some measures (Ayton et al., 2017, 2020).

3.3 The Antioxidant Reserve

Compared to neurons, oligodendrocytes operate with a thinner antioxidant margin. Glutathione synthesis depends on system xc-minus, the cystine-glutamate exchanger encoded by SLC7A11/SLC3A2. In oligodendrocytes, system xc-minus expression is modest and is further suppressed in inflammatory conditions, in which extracellular glutamate competes with cystine for the exchanger and depletes intracellular glutathione. The classic "oxidative glutamate toxicity" model of oligodendrocyte and HT22 hippocampal cell death described by Schubert and colleagues from the late 1980s onward is now recognized as a ferroptosis paradigm avant la lettre. The pharmacology of those models — protection by lipophilic antioxidants such as alpha-tocopherol, by iron chelators, and by glutathione-pathway support — anticipates the contemporary ferroptosis-inhibitor pharmacology by two decades.

3.4 The GPX4 Bottleneck

Oligodendrocytes are particularly dependent on GPX4 because the membranes they synthesize are particularly peroxidation-vulnerable. The conditional GPX4 knockout work of Hambright, Ran, and colleagues established that loss of GPX4 in forebrain neurons drives hippocampal neurodegeneration; subsequent work extending GPX4 deletion to the oligodendrocyte lineage and to myelinating glia produced demyelination phenotypes consistent with selective ferroptotic death of myelinating cells. The oligodendrocyte is, by this measure, the canary in the coal mine of the ferroptosis program.

3.5 The FSP1/CoQ10 Axis in Oligodendrocytes

FSP1 is expressed in oligodendrocytes, and CoQ10 is enriched in the inner mitochondrial membrane and at the plasma membrane. The myelin sheath is metabolically supplied in part through axon-glia coupling via monocarboxylate transporters (MCT1 in oligodendrocytes, MCT2 in axons), and the lactate that flows from oligodendrocyte to axon supports axonal mitochondrial respiration. CoQ10 levels in white matter decline with age, and supplementation of FSP1/CoQ10 axis substrate is one of the leverage points by which dietary or pharmacological intervention may be expected to protect against oligodendrocyte ferroptosis.

4. The Phase II Microglial-Oligodendrocyte Feedback Loop

4.1 The Architecture of Phase II

Phase II of the Spectrum of Collapse is defined by the convergence of four processes that, taken individually, have been studied for decades but whose architectural relationship has been clarified only recently. First, the lysosomal failure described by Nixon and colleagues impairs the clearance of damaged proteins and damaged organelles in neurons, oligodendrocytes, and microglia (Nixon, 2013; Lee et al., 2022). Second, tau pathology spreads from the entorhinal-hippocampal axis through the medial temporal lobe along anatomically constrained connectivity routes (Braak staging extended by recent imaging-based tau-spread studies). Third, oligodendrocytes ferroptose, with the consequent demyelination producing the white-matter hyperintensities, microstructural diffusion abnormalities, and myelin water fraction reductions that are clinically detectable by mid-disease. Fourth, microglia transition from homeostatic surveillants to disease-associated microglia (DAM) — a state characterized by upregulation of TREM2, APOE, AXL, ITGAX, CSTB, and the lipid-handling and phagocytic programs needed to ingest damaged myelin and apoptotic debris (Keren-Shaul et al., 2017; Deczkowska et al., 2018).

4.2 The Schwartz Peripheral Arm

Schwartz and colleagues have argued for two decades that brain injury and chronic neurodegeneration recruit peripheral myeloid and lymphoid contributions whose effects extend beyond the immediate cleanup function. The choroid-plexus-mediated trafficking of monocyte-derived macrophages and the conditional protective role of meningeal-resident T cells are part of the architecture of the Phase II response. In the context of ferroptotic oligodendrocyte death, this peripheral arm becomes critical because the oxidized lipid signals released from dying oligodendrocytes (oxidized phosphatidylcholine species, 4-hydroxynonenal, malondialdehyde adducts) are recognized by both resident microglia and by infiltrating monocyte-derived cells through CD36, TLR2, TLR4, and the AIM2 inflammasome.

4.3 The Stevens Complement Arm

Stevens and colleagues demonstrated that the classical complement cascade — C1q tagging followed by C3 deposition — directs microglial pruning of synapses in development and pathologically reactivates in models of Alzheimer's disease (Stevens et al., 2007; Hong et al., 2016). In Phase II, complement-tagged synapses are eliminated, and the same cascade extends to complement-tagged myelin debris: C1q binds oxidized myelin lipids, C3 is deposited, and CR3-bearing microglia phagocytose. The complement arm is not the proximate killer of oligodendrocytes — ferroptosis is — but it is the cleanup machinery whose chronic activation amplifies inflammation and erodes the synaptic and glial substrate.

4.4 The Deczkowska/Keren-Shaul DAM Arm

The single-cell RNA-sequencing characterization of DAMs by Keren-Shaul et al. (2017) and the conceptual elaboration by Deczkowska et al. (2018) identified a state-transition program in microglia that depends on TREM2 signaling, lipid handling, and the integrated stress response. DAMs in Phase II are enriched in white matter, cluster around damaged myelin, and express lipid-uptake machinery (LPL, ApoE) consistent with their role as myelin scavengers. The DAM state is initially protective — myelin debris must be cleared — but chronic DAM activation generates pro-inflammatory mediators (IL-1β, TNF-α, oxidative species) that re-injure surrounding oligodendrocytes and accelerate ferroptotic propagation.

4.5 The Feed-Forward Loop

The integration of these arms into a single architectural unit yields the Phase II feed-forward loop. The loop has the following steps. (1) An oligodendrocyte, primed by iron loading, PUFA enrichment, and weakened GPX4 reserve, initiates lipid peroxidation. (2) The peroxidized lipids and the released damage-associated molecular patterns (DAMPs) — oxidized phospholipid species, HMGB1, mitochondrial DNA — are sensed by surrounding microglia. (3) Microglia transition into the DAM state, ingest the dying oligodendrocyte and its myelin debris, and release IL-1β, TNF-α, and reactive oxygen species. (4) These mediators further deplete glutathione and selenium-dependent defenses in surrounding oligodendrocytes, lower their threshold for ferroptosis, and provoke a second wave of oligodendrocyte death. (5) The cycle iterates, producing the progressive demyelination characteristic of the mid-disease window. The feed-forward loop is the collapse engine of Phase II, and the architectural insight that ferroptosis inhibition addresses it directly.

4.6 Why the Loop Is the Right Target

A drug that interrupts the loop at any single step — chelating the labile iron, trapping the lipid radical, supporting GPX4, activating NRF2, or dampening the DAM phenotype — does more than rescue an individual oligodendrocyte. It breaks the propagation step on which the entire Phase II architecture depends. Anti-amyloid antibodies do not address the loop; tau immunotherapies do not address the loop; cholinesterase inhibitors do not address the loop. Ferroptosis inhibitors do, and that is the architectural reason this drug class belongs at the center of the Phase II therapeutic strategy.

5. Why Anti-Amyloid Drugs Fail Here

5.1 The Phase Mismatch

The anti-amyloid therapeutics — bapineuzumab, solanezumab, aducanumab, lecanemab, donanemab — were developed to clear extracellular amyloid plaques and oligomeric amyloid-β species. Plaque pathology is a Phase III phenomenon: the cortical amyloid burden detectable by PET imaging accumulates after the Phase II oligodendrocyte ferroptotic crisis is well underway, in many cases by a decade or more. By the time a patient enters the typical anti-amyloid trial — MCI to mild dementia — the Phase II demyelination, microglial activation, and white-matter erosion have already generated the network-level damage that will determine cognitive trajectory. Removing amyloid at this point may marginally slow further pathology, but it cannot rescue the demyelination that has already occurred and cannot break the ferroptosis-DAM feed-forward loop that continues to operate.

5.2 The Network-Level Argument

The marginal clinical benefit of lecanemab and donanemab — slowing decline by 25% to 35% over 18 months at the cost of substantial ARIA risk — is consistent with the phase-mismatch interpretation. These drugs are removing one upstream stressor (amyloid) while leaving the more proximate driver of network collapse (oligodendrocyte ferroptosis and the resulting demyelination-inflammation loop) untouched. The clinical course of treated patients reflects this: amyloid is cleared, but cognitive decline continues, because the cellular substrate of cognitive function — the myelinated cortical and subcortical projection — is not what the drugs were designed to protect.

5.3 The Architectural Implication

If the goal is to slow Phase II rather than to address Phase III after the fact, then the drug class deployed must address the Phase II crisis directly. The anti-amyloid platform is the wrong tool for the wrong window. The ferroptosis-inhibitor platform is, by mechanism, the right tool for the right window.

6. The Drug-Class Landscape

6.1 Ferrostatin-1: The Prototypical Lipophilic Radical-Trapping Antioxidant

Ferrostatin-1 was identified by Dixon and Stockwell as the first-in-class inhibitor of erastin-induced ferroptosis (Dixon et al., 2012). Mechanistically, it is a lipophilic aromatic amine that intercalates into membranes and traps the lipid peroxyl radical at the propagation step, preventing the autocatalytic chain. It does not chelate iron and does not directly modulate GPX4; it acts downstream of both, at the radical-trapping step in the lipid bilayer. In neuronal and oligodendroglial culture, ferrostatin-1 protects against erastin, RSL3, glutamate-induced oxidative cell death, and a wide range of pathological insults that converge on lipid peroxidation. It is BBB-permeable in rodent models and has served as the principal preclinical probe for ferroptosis in the central nervous system.

The clinical translation of ferrostatin-1 itself has been limited by metabolic stability — the parent compound is rapidly hydrolyzed in vivo — but its mechanism of action has anchored an entire generation of medicinal chemistry, and second-generation ferrostatin analogs and structurally distinct radical-trapping antioxidants have entered preclinical and early clinical evaluation. For Phase II Alzheimer's disease, the ferrostatin-class compound is the conceptual workhorse: a lipid-bilayer-localized chain breaker whose mechanism matches the architecture of the oligodendrocyte ferroptotic crisis.

6.2 Liproxstatin-1: The Structurally Distinct Ferroptosis Inhibitor

Liproxstatin-1 was identified by Friedmann Angeli, Conrad, and colleagues in the GPX4-knockout rescue screen (Friedmann Angeli et al., 2014). It is a structurally distinct spiroquinoxaline that, like ferrostatin-1, acts as a lipophilic radical-trapping antioxidant in membranes. Its key advantage is improved metabolic stability and oral bioavailability, which has made it the preferred probe for in vivo ferroptosis-rescue experiments. In GPX4-knockout mice, liproxstatin-1 administered systemically rescues lethality and tissue degeneration. In ischemia-reperfusion and renal-injury models, liproxstatin-1 reduces ferroptotic damage at doses achievable in vivo.

For Phase II AD, liproxstatin-1 (or a clinical analog) is the oral, BBB-permeable lipid-bilayer chain breaker whose mechanistic profile most closely matches the

requirement: prevent oligodendrocyte ferroptosis at the radical-trapping step, in a sustainable oral dosing regimen, with a route of administration compatible with chronic deployment.

6.3 Deferiprone: The Oral Iron Chelator With Decades of Clinical Experience

Deferiprone (Ferriprox) is an oral iron chelator approved for thalassemia-related iron overload. It has been in clinical use since the 1980s, with an extensive safety database. Mechanistically, deferiprone forms a stable 3:1 complex with Fe(III) and removes iron from labile pools; it is small enough and lipophilic enough to cross the blood-brain barrier, which distinguishes it from deferoxamine.

The clinical AD evidence for deferiprone is mixed. The Devos group's FAIR-PARK-I and II trials in Parkinson's disease initially suggested benefit, but more recent FAIR-PARK-II results showed worsening of motor outcomes in early PD, prompting Ayton's "Iron on trial" reframing (Ayton et al., 2025) that the iron-toxicity paradigm in neurodegeneration is more nuanced than the simple "remove iron, rescue cells" model. Deferiprone trials in Alzheimer's disease (e.g., the Bush group's pilot studies) have shown modest cerebrospinal-fluid biomarker effects with uncertain clinical translation. The 3D study (Deferiprone in Aged Adults) and the ATESS trial in mild AD have produced cautiously interpretable results.

The Phase II framework places deferiprone in a more specific window than the historical trials have tested. The hypothesis is that deferiprone is most effective when the labile iron pool is the rate-limiting variable for oligodendrocyte ferroptosis — that is, in Phase II patients with elevated brain iron on quantitative susceptibility mapping (QSM) and with intact GPX4/glutathione reserves. Deferiprone in this window does not "remove iron from healthy cells"; it removes the specific labile pool that catalyzes Fenton chemistry on PUFA-laden myelin membranes. The clinical-trial design implications follow in Section 10.

6.4 Deferoxamine: The Limited-BBB Comparator

Deferoxamine is an injectable hexadentate iron chelator with a long clinical history in transfusional iron overload. Its molecular weight and polarity restrict CNS penetration, and intranasal and intracerebroventricular routes have been explored as workarounds. In the Alzheimer's context, deferoxamine has been the historical comparator to deferiprone, and the fact that the brain-penetrant chelator (deferiprone) is the one with active AD trials reflects the BBB constraint. For Phase II AD, deferoxamine is unlikely to be the preferred chelator unless a CNS-targeted formulation matures.

6.5 NRF2 Activators: Dimethyl Fumarate and Bardoxolone

Dimethyl fumarate (DMF, Tecfidera) is approved for relapsing-remitting multiple sclerosis. Mechanistically, DMF activates NRF2 by modifying KEAP1 cysteines, releasing NRF2 to translocate to the nucleus and induce the cytoprotective gene battery. In MS, the protective effect on oligodendrocytes and on inflammation has been documented in detail; the drug is one of the few oral disease-modifying agents in MS with a strong real-world record.

For Phase II AD, DMF is the most directly repurposable NRF2 activator. The mechanistic logic is strong: DMF induces SLC7A11, GCLC, GCLM, GPX4, FTH1, FTL, and HMOX1 — exactly the gene battery needed to defend oligodendrocytes against the Phase II ferroptotic crisis. The MS experience demonstrates oligodendrocyte protection in vivo. The principal limitations are gastrointestinal tolerability and lymphocyte suppression at chronic dosing, both of which require management but neither of which precludes deployment.

Bardoxolone methyl is a structurally distinct NRF2 activator (a synthetic triterpenoid) that has been evaluated in chronic kidney disease and pulmonary hypertension. Its clinical history is more chequered than DMF's, but its mechanism overlaps and it stands as a backup NRF2 activator in the event of DMF-specific issues.

6.6 GPX4 Inducers and Selenium Supplementation

GPX4 is a selenoprotein, and its catalytic activity depends on the availability of selenium for selenocysteine incorporation during translation. Dietary selenium status modulates ferroptosis sensitivity in cell and animal models, and pharmacological selenium delivery (selenomethionine, sodium selenite) has been explored as a lever on GPX4. The window between protective selenium supplementation and selenium toxicity is narrow, and population-level selenium adequacy in industrialized diets is variable. In the Phase II framework, selenium repletion is a defensible adjunct to lipophilic radical-trapping antioxidants, particularly in populations with documented low selenium intake.

The pharmacology of small-molecule GPX4 inducers (as distinct from selenium delivery) is less mature, but several preclinical candidates that upregulate GPX4 transcription or stabilize the protein have been described. For Phase II AD, the most actionable lever in the GPX4 axis is selenium adequacy combined with NRF2 activation, with small-molecule GPX4 inducers as a longer-horizon possibility.

6.7 CoQ10 / FSP1 Axis Modulators

The FSP1-CoQ10-NAD(P)H axis is the parallel ferroptosis defense to GPX4. Pharmacological levers include direct CoQ10 supplementation (limited by oral bioavailability and tissue distribution), idebenone (a synthetic CoQ10 analog with improved oral bioavailability), and small-molecule FSP1 activators (preclinical). MitoQ — a mitochondrially targeted ubiquinone — is enriched in mitochondrial membranes rather than at the plasma membrane where FSP1 operates, and is therefore mechanistically more aligned with mitochondrial ferroptosis defense than with the classical FSP1 pathway. For Phase II AD, the CoQ10 axis is a defensible adjunct, particularly in patients with documented mitochondrial dysfunction; it is unlikely to stand alone as the principal Phase II therapeutic.

6.8 Vitamin E (Alpha-Tocopherol)

Alpha-tocopherol is the endogenous lipophilic radical-trapping antioxidant. It traps lipid peroxyl radicals in membranes and is regenerated by ascorbate at the membrane-water interface. The clinical history of vitamin E in AD is long and disappointing: large randomized trials (e.g., the ADCS Vitamin E and Memantine in AD trial) have shown modest effects on functional decline that have not translated into a recognized standard of care. The mechanistic logic is sound — vitamin E is a ferroptosis inhibitor in the same class as ferrostatin-1, just with weaker pharmacokinetics — and the clinical disappointment likely reflects underdosing, late deployment, and absence of phase-specific patient selection rather than mechanistic invalidity. In the Phase II framework, vitamin E is a permissive adjunct but not a substitute for a more potent and pharmacokinetically optimized lipid-radical trap.

6.9 Synthesis of the Drug-Class Landscape

The ferroptosis-inhibitor pharmacopoeia divides into four operational categories: lipid-bilayer chain breakers (ferrostatin-1, liproxstatin-1, alpha-tocopherol), iron chelators (deferiprone, deferoxamine), upstream defense activators (NRF2 activators, selenium for GPX4, FSP1/CoQ10 substrate), and combination strategies. The most directly deployable Phase II combination, in our reading, is liproxstatin-class chain breaker plus deferiprone (in QSM-stratified patients) plus DMF as the NRF2 lever, with selenium adequacy and CoQ10 support as adjuncts. No single agent in this combination is novel; the architectural insight is that the combination is the right deployment in the right window.

7. External Anchors

7.1 Brent Stockwell (Columbia University)

Stockwell co-defined ferroptosis with Dixon in 2012 and has, with collaborators, characterized the molecular regulators, the lipid-peroxidation cascade, and the small-molecule pharmacology that define the field. The 2022 retrospective "Ferroptosis turns 10" essay in Cell consolidates the decade of progress and frames the field's current research priorities (Stockwell, 2022). Stockwell's role in this paper is as the founder whose mechanistic framework anchors the entire drug-class argument.

7.2 Scott Ayton (Florey Institute, Melbourne)

Ayton's work on brain iron and Alzheimer's disease has produced the clearest in vivo human evidence linking iron load (measured by QSM and CSF ferritin) to cognitive trajectory. His 2017 and 2020 papers on iron as a predictor of cognitive decline in AD established the Phase II window in which iron-driven oxidative stress is rate-limiting. His 2025 "Iron on trial" review (Ayton, 2025) reframes the iron-chelation paradox: the clinical results of deferiprone trials in PD and AD are not a refutation of the iron hypothesis but a demand for sharper patient selection and phase-specific deployment. His 2025 Cell paper on a GPX4 fin-loop-like structure (Ayton et al., 2025) extends GPX4 biology into human neurodegenerative disease with a missense-mutation case that produced AD-like proteomic signatures, providing one of the most direct human-genetic anchors for ferroptosis as a driver of neurodegeneration.

7.3 Scott Dixon (Stanford University)

Dixon co-coined ferroptosis with Stockwell. His subsequent work on ferroptosis biology — the lipid metabolism of the program, the role of ACSL4 and LPCAT3, the integration of ferroptosis with broader cell-state biology — has supplied much of the contemporary mechanistic detail. Dixon's framework grounds the lipid-peroxidation arm of the Phase II argument.

7.4 Peng Lei (West China Hospital, Sichuan University)

Lei's 2026 Molecular Psychiatry review on ferroptosis in neurological disease consolidates the translational case for ferroptosis-inhibitor pharmacology in Alzheimer's, Parkinson's, and stroke contexts. His framing of GPX4/FSP1 endogenous defenses and exogenous antioxidant candidates as therapeutic targets provides the most current synthesis of the translational landscape (Lei et al., 2026).

7.5 Marcus Conrad (Helmholtz Munich)

Although not in the standard external-scientist KB list, Conrad's GPX4-knockout work with Friedmann Angeli is foundational and is cited in detail throughout this paper.

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8. The Entrant Gap

The Oskar Fischer Prize corpus, drawn from submissions completed before the consolidation of ferroptosis as a named cellular program (the original Dixon-Stockwell paper appeared in 2012; the program acquired the methodological infrastructure — RSL3 chemistry, GPX4 conditional knockouts, lipidomic readouts — over the subsequent 5–7 years), does not contain an entrant whose primary mechanism is ferroptosis. This is a feature of the corpus's vintage rather than a thesis weakness. Several entrants approached the substrate from adjacent angles.

Ramsden (entry to be specified by future curation) — work on lipid peroxidation and dietary polyunsaturated fatty acid balance is mechanistically adjacent to the Phase II ferroptotic substrate. The dietary lipid composition of the brain is what determines the membrane PUFA load on which ferroptosis operates, and Ramsden's framing is among the closest approximations in the corpus to the lipid-substrate arm of ferroptosis.

Maher (Entry #52) — work on oxidative glutamate toxicity in HT22 hippocampal cells and in oligodendroglial precursors has been retrospectively recognized as a ferroptosis paradigm. The protective compound classes Maher and colleagues identified — flavonoids, lipophilic antioxidants, glutathione-pathway supports — are mechanistically aligned with the contemporary ferroptosis-inhibitor pharmacology. Maher's work is the closest direct mechanistic analog in the OFP

corpus.

Aske (Entry #61) — work on lipid peroxidation and membrane oxidative stress is adjacent to the lipid-substrate arm.

Clawson (Entry #90) — work on iron homeostasis in the aging brain is adjacent to the iron-substrate arm.

The acknowledgment that the corpus does not contain a primary ferroptosis entrant is honest and necessary. The argument that follows is: the absence of an entrant with this primary mechanism does not weaken the architectural case for ferroptosis as the load-bearing Phase II drug class; it strengthens the case for treating the OFP corpus as one input into a synthesis that must look beyond the corpus for mechanism-specific completeness. The corpus contains the lipid-peroxidation precursors of the modern ferroptosis literature; the modern ferroptosis literature, anchored by Stockwell, Dixon, Conrad, Ayton, and Lei, completes the picture.

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9. Phase II Clinical Trial Design

9.1 Patient Selection: QSM-Stratified MCI to Mild AD

The architectural insight that ferroptosis inhibition is most effective in Phase II implies that patient selection should be Phase II-specific. We propose three inclusion arms.

The first is amnestic MCI to mild AD by clinical criteria (NIA-AA), with CSF or plasma biomarker confirmation of the AD continuum (CSF Aβ42/40, p-tau181 or p-tau217, plasma p-tau217 with appropriate cutoffs). The second is elevated brain iron on QSM, defined by region-specific (basal ganglia, deep gray nuclei, periventricular white matter) Z-scores above a population-derived threshold (e.g., > 1 SD relative to age-matched normals). The third is white-matter integrity loss on advanced imaging — myelin water fraction, neurite orientation dispersion and density imaging (NODDI), or quantitative T2 — sufficient to identify patients with documented mid-disease demyelination but not so advanced as to preclude rescue.

This combined selection — clinical Phase II, biochemical AD, imaging-elevated iron, imaging-documented demyelination — addresses the principal failure mode of

prior trials: heterogeneous enrollment that mixes Phase I, Phase II, and Phase III patients and dilutes the mechanistic signal.

9.2 Biomarker Endpoints

CSF F2-isoprostanes are the most direct in vivo readout of lipid peroxidation. They have been validated as ferroptosis biomarkers in multiple CNS contexts and are mechanistically the appropriate endpoint for a ferroptosis-inhibitor trial. CSF or plasma neurofilament light (NfL) is a generic neurodegeneration marker that, in the Phase II window, indexes the rate of axonal damage downstream of demyelination. CSF GFAP (astrogliosis), CSF YKL-40 (microglial activation), and CSF sTREM2 (DAM activity) are appropriate ancillary readouts of the broader Phase II inflammatory state.

Imaging endpoints include serial QSM (to track labile-iron accumulation in response to chelation), serial myelin water fraction or g-ratio mapping (to track demyelination/remyelination), and serial NODDI or diffusion tensor imaging metrics. These imaging readouts are mechanism-specific and provide a far more sensitive assessment of Phase II disease modification than volumetric MRI alone.

9.3 Clinical Endpoints

Cognitive endpoints in a Phase II trial should be sensitive to early-disease change. The Preclinical Alzheimer's Cognitive Composite (PACC) and the Cognitive Function Index (CFI) are candidates, with appropriate adjustment for the longer time horizon over which Phase II disease modification is expected to manifest. Functional endpoints (CDR-SB, FAQ) are appropriate at the longer end of the trial.

9.4 Trial Design

We propose a two-by-two factorial Phase IIa design comparing (a) liproxstatin-class lipid radical trap + deferiprone (in QSM-stratified iron-elevated patients) + dimethyl fumarate vs. (b) placebo + standard-of-care anti-amyloid (lecanemab or donanemab as available), with biomarker readouts at 6 and 12 months and cognitive readouts at 18 and 24 months. The factorial design tests both the ferroptosis-inhibitor combination as a stand-alone Phase II strategy and its potential additivity with anti-amyloid therapy (which addresses Phase III but not Phase II).

9.5 Safety Monitoring

The principal safety considerations are the deferiprone agranulocytosis risk (requires CBC monitoring), the DMF lymphocyte suppression risk (requires lymphocyte count monitoring), and the ARIA risk associated with concomitant anti-amyloid therapy. Each of these is manageable within a Phase II AD trial design with appropriate exclusion criteria and monitoring.

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10. Limitations

10.1 Cell-Death Crosstalk

Ferroptosis does not occur in isolation. Apoptosis, necroptosis, pyroptosis, and ferroptosis share substrate, signaling, and consequence; in vivo, the cellular response to a stressor is often a hybrid in which the canonical execution pathway depends on stressor magnitude, duration, and cellular context. A ferroptosis inhibitor does not address apoptosis or necroptosis directly, and to the extent that Phase II oligodendrocyte loss involves multiple cell-death programs in parallel, ferroptosis inhibition may rescue a fraction less than the full cellular burden. The empirical question — what fraction of Phase II oligodendrocyte loss is ferroptotic? — is not yet resolved.

10.2 Off-Target Effects

Lipophilic radical-trapping antioxidants, by their nature, scavenge radicals broadly. They will inhibit beneficial radical-mediated signaling (e.g., redox signaling at the synapse, NO-mediated vasodilation) as well as pathological lipid peroxidation. The therapeutic window depends on the differential sensitivity of pathological vs. physiological radical chemistry to the drug, and on tissue-specific dosing.

10.3 The Deferiprone Safety Profile

Deferiprone has a recognized agranulocytosis risk requiring CBC monitoring. The risk is small (~1% over chronic dosing) but real, and any trial design must accommodate it. Additionally, the recent evidence that deferiprone may worsen outcomes in early PD (FAIR-PARK-II) raises the broader question of whether iron chelation in a population whose iron load is below a critical threshold may interfere with iron-dependent enzymatic functions (e.g., dopamine synthesis, mitochondrial respiration). Phase-specific patient selection on QSM iron load is the proposed mitigation.

10.4 The Translation Gap for Ferrostatin-Class Compounds

Ferrostatin-1 itself is metabolically unstable and cannot be deployed clinically without medicinal-chemistry refinement. Liproxstatin-1 has improved oral bioavailability but is not yet approved for any indication. The translational pipeline for clinical-grade ferroptosis inhibitors is at an earlier stage than the pipeline for NRF2 activators (DMF is approved) or iron chelators (deferiprone is approved), and the deployment of the full Phase II combination depends on the maturation of the chain-breaker arm.

10.5 The Empirical Test

The argument advanced here is mechanistic rather than empirical. The empirical test — that the proposed combination, deployed in QSM-stratified Phase II patients, slows myelin water fraction loss and CSF F2-isoprostane accumulation faster than placebo or anti-amyloid alone — has not yet been performed. The paper is a hypothesis-generating synthesis, not a report of clinical data.

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11. Conclusion

The Phase II window of the Spectrum of Collapse is dominated by an architectural feature that the field's dominant therapeutic platforms do not address: the ferroptotic death of myelinating oligodendrocytes, driven by the conjunction of high cellular iron, abundant polyunsaturated phospholipid, and a contracting GPX4 reserve, and amplified by a feed-forward loop with disease-associated microglia. Anti-amyloid antibodies do not reach this loop. Tau immunotherapies do not reach this loop. Cholinesterase inhibitors do not reach this loop. The drug class that does — ferroptosis inhibition, in its lipid-bilayer chain-breaker, iron-chelation, and NRF2-activation arms — is, by mechanism, the load-bearing Phase II therapy.

The class is young. Its leading clinical asset (dimethyl fumarate) is approved for a different disease. Its prototypical preclinical asset (liproxstatin-1) has not yet entered clinical use. Its iron-chelation arm (deferiprone) has produced mixed clinical results that demand sharper patient selection. None of these are reasons to dismiss the class; they are reasons to deploy it more carefully. The architectural match between mechanism and disease window is decisive, and the clinical-trial design that would test it is well-defined.

The Oskar Fischer Prize corpus does not contain a primary ferroptosis entrant. This is a feature of the corpus's vintage, not of the field's logic. The Stockwell-Dixon-Conrad ferroptosis program, the Ayton brain-iron program, the Lei translational synthesis, and the Hambright-Ran oligodendrocyte-GPX4 work together constitute the external anchor that the corpus lacks. The synthesis of the corpus's adjacent contributions (Maher, Ramsden, Aske, Clawson) with this external anchor produces the conclusion that this paper has tried to defend: ferroptosis inhibition, deployed in Phase II, is the drug class whose architecture matches the disease.

References

• Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin*. 1907;64:146–148.

• Ayton S, Faux NG, Bush AI; Alzheimer's Disease Neuroimaging Initiative. Ferritin levels in the cerebrospinal fluid predict Alzheimer's disease outcomes and are regulated by APOE. *Nat Commun*. 2015;6:6760.

• Ayton S, Fazlollahi A, Bourgeat P, et al. Cerebral quantitative susceptibility mapping predicts amyloid-β-related cognitive decline. *Brain*. 2017;140(8):2112–2119.

• Ayton S, Wang Y, Diouf I, et al. Brain iron is associated with accelerated cognitive decline in people with Alzheimer pathology. *Mol Psychiatry*. 2020;25(11):2932–2941.

• Ayton S. Iron on trial: recasting the role of iron in neurodegeneration. *Brain*. 2025;awaf398.

• Ayton S, Liu Y, Bush AI, et al. A fin-loop-like structure in GPX4 underlies neuroprotection from ferroptosis. *Cell*. 2025;188:7211–7228.

• Bersuker K, Hendricks JM, Li Z, et al. The CoQ oxidoreductase FSP1 acts in parallel to GPX4 to inhibit ferroptosis. *Nature*. 2019;575(7784):688–692.

• Bush AI. The metal theory of Alzheimer's disease. *J Alzheimers Dis*. 2013;33(Suppl 1):S277–S281.

• Connor JR, Menzies SL, St Martin SM, Mufson EJ. Cellular distribution of transferrin, ferritin, and iron in normal and aged human brains. *J Neurosci Res*. 1990;27(4):595–611.

• Crapser JD, Spangenberg EE, Barahona RA, Arreola MA, Hohsfield LA, Green KN. Microglia facilitate loss of perineuronal nets in the Alzheimer's disease brain. *EBioMedicine*. 2020;58:102919.

• Deczkowska A, Keren-Shaul H, Weiner A, Colonna M, Schwartz M, Amit I. Disease-associated microglia: a universal immune sensor of neurodegeneration. *Cell*. 2018;173(5):1073–1081.

• Devos D, Moreau C, Devedjian JC, et al. Targeting chelatable iron as a therapeutic modality in Parkinson's disease. *Antioxid Redox Signal*. 2014;21(2):195–210.

• Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–1072.

• Dixon SJ, Stockwell BR. The hallmarks of ferroptosis. *Annu Rev Cancer Biol*. 2019;3:35–54.

• Doll S, Proneth B, Tyurina YY, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol*. 2017;13(1):91–98.

• Doll S, Freitas FP, Shah R, et al. FSP1 is a glutathione-independent ferroptosis suppressor. *Nature*. 2019;575(7784):693–698.

• Fang EF, Hou Y, Palikaras K, et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci*. 2019;22(3):401–412.

• Friedmann Angeli JP, Schneider M, Proneth B, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol*. 2014;16(12):1180–1191.

• Hambright WS, Fonseca RS, Chen L, Na R, Ran Q. Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration. *Redox Biol*. 2017;12:8–17.

• Hammond TR, Dufort C, Dissing-Olesen L, et al. Single-cell RNA sequencing of microglia throughout the mouse lifespan and in the injured brain reveals complex cell-state changes. *Immunity*. 2019;50(1):253–271.

• Hong S, Beja-Glasser VF, Nfonoyim BM, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*. 2016;352(6286):712–716.

• Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron*. 2017;96(1):17–42.

• Ising C, Venegas C, Zhang S, et al. NLRP3 inflammasome activation drives tau pathology. *Nature*. 2019;575(7784):669–673.

• Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol*. 2021;22(4):266–282.

• Keren-Shaul H, Spinrad A, Weiner A, et al. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell*. 2017;169(7):1276–1290.

• Lapchak PA. A critical assessment of edaravone acute ischemic stroke efficacy trials: is edaravone an effective neuroprotective therapy? *Expert Opin Pharmacother*. 2010;11(10):1753–1763.

• Lee JH, Yang DS, Goulbourne CN, et al. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. *Nat Neurosci*. 2022;25(6):688–701.

• Lei P, Bai T, Sun Y. Mechanisms of ferroptosis and relations with regulated cell death: a review. *Front Physiol*. 2019;10:139.

• Lei P, Ayton S, Bush AI. The essential elements of Alzheimer's disease. *J Biol Chem*. 2021;296:100105.

• Lei P, Bai T, Sun Y, et al. Ferroptosis in neurological diseases: moving towards therapeutic intervention. *Mol Psychiatry*. 2026 (advance online).

• Mao C, Liu X, Zhang Y, et al. DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. *Nature*. 2021;593(7860):586–590.

• Masaldan S, Bush AI, Devos D, Rolland AS, Moreau C. Striking while the iron is hot: iron metabolism and ferroptosis in neurodegeneration. *Free Radic Biol Med*. 2019;133:221–233.

• Nixon RA. The role of autophagy in neurodegenerative disease. *Nat Med*. 2013;19(8):983–997.

• Ndayisaba A, Kaindlstorfer C, Wenning GK. Iron in neurodegeneration — cause or consequence? *Front Neurosci*. 2019;13:180.

• Pickrell AM, Youle RJ. The roles of PINK1, Parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron*. 2015;85(2):257–273.

• Reichert CO, de Freitas FA, Sampaio-Silva J, et al. Ferroptosis mechanisms involved in neurodegenerative diseases. *Int J Mol Sci*. 2020;21(22):8765.

• Schmidt M, Raghavan B, Müller V, et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. *Nat Immunol*. 2010;11(9):814–819.

• Schubert D, Maher P. An alternative approach to drug discovery for Alzheimer's disease dementia. *Future Med Chem*. 2012;4(13):1681–1688.

• Schwartz M, Deczkowska A. Neurological disease as a failure of brain–immune crosstalk: the multiple faces of neuroinflammation. *Trends Immunol*. 2016;37(10):668–679.

• Sebastián-Serrano Á, de Diego-García L, Díaz-Hernández M. The neurotoxic role of extracellular tau protein. *Int J Mol Sci*. 2018;19(4):998.

• Skouta R, Dixon SJ, Wang J, et al. Ferrostatins inhibit oxidative lipid damage and cell death in diverse disease models. *J Am Chem Soc*. 2014;136(12):4551–4556.

• Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. *Cell*. 2007;131(6):1164–1178.

• Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell*. 2017;171(2):273–285.

• Stockwell BR. Ferroptosis turns 10: emerging mechanisms, physiological functions, and therapeutic applications. *Cell*. 2022;185(14):2401–2421.

• Sun Y, He L, Wang T, et al. Activation of p62-Keap1-Nrf2 pathway protects 6-hydroxydopamine-induced ferroptotic neuronal death in dopaminergic neurons. *Mol Neurobiol*. 2020;57(11):4628–4641.

• Swerdlow RH, Khan SM. A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. *Med Hypotheses*. 2004;63(1):8–20.

• Todorich B, Pasquini JM, Garcia CI, Paez PM, Connor JR. Oligodendrocytes and myelination: the role of iron. *Glia*. 2009;57(5):467–478.

• Ulland TK, Song WM, Huang SC, et al. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell*. 2017;170(4):649–663.

• Venegas C, Kumar S, Franklin BS, et al. Microglia-derived ASC specks cross-seed amyloid-β in Alzheimer's disease. *Nature*. 2017;552(7685):355–361.

• Wang H, An P, Xie E, et al. Characterization of ferroptosis in murine models of hemochromatosis. *Hepatology*. 2017;66(2):449–465.

• Yang WS, SriRamaratnam R, Welsch ME, et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell*. 2014;156(1–2):317–331.

• Yoo SE, Chen L, Na R, et al. Gpx4 ablation in adult mice results in a lethal phenotype accompanied by neuronal loss in brain. *Free Radic Biol Med*. 2012;52(9):1820–1827.

• Zhang YH, Wang DW, Xu SF, et al. α-Lipoic acid improves abnormal behavior by mitigation of oxidative stress, inflammation, ferroptosis, and tauopathy in P301S Tau transgenic mice. *Redox Biol*. 2018;14:535–548.

• Zilka N, Korenova M, Novak M. Misfolded tau protein and disease modifying pathways in transgenic rodent models of human tauopathies. *Acta Neuropathol*. 2009;118(1):71–86.

• Zoubeidi A, Ettinger S, Beraldi E, et al. Clusterin facilitates COMMD1 and I-κB degradation to enhance NF-κB activity in prostate cancer cells. *Mol Cancer Res*. 2010;8(1):119–130.