



NecroFerrins as dual therapeutic inhibitors targeting necroptosis and ferroptosis

Claire Delehouzé^{1,*}, Stéphane Bach^{2,3,*}

¹SeaBeLife Biotech, Place Georges Teissier, Roscoff 29680, France.

²Sorbonne Université, CNRS, UMR8227, Integrative Biology of Marine Models Laboratory (LBI2M), Station Biologique de Roscoff, Roscoff 29680, France.

³Sorbonne Université, CNRS, FR2424, Plateforme de criblage KISSf (Kinase Inhibitor Specialized Screening facility), Station Biologique de Roscoff, Roscoff 29680, France.

***Correspondence to:** Claire Delehouzé, SeaBeLife Biotech, Place Georges Teissier, Roscoff 29680, France. E-mail: claire.delehouze@seabelife.com

Stéphane Bach, Sorbonne Université, CNRS, UMR8227, Integrative Biology of Marine Models Laboratory (LBI2M), Station Biologique de Roscoff, Roscoff 29680, France; Sorbonne Université, CNRS, FR2424, Plateforme de criblage KISSf (Kinase Inhibitor Specialized Screening facility), Station Biologique de Roscoff, Roscoff 29680, France. E-mail: bach@sb-roscoff.fr

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Abstract

Over the past two decades, increasing attention has been devoted to regulated forms of cell death that occur independently of apoptosis. Among these, necroptosis and ferroptosis exhibit a necrotic-like morphology, yet are defined by distinct molecular and biochemical signatures. Both pathways have attracted considerable interest due to growing evidence implicating them in the pathogenesis of a wide range of acute and chronic disorders. Notably, the simultaneous engagement of multiple regulated necrosis pathways has been reported in many disease contexts, highlighting the limitations of single-target therapeutic approaches. In this light, the design of multi-target-directed ligands, that is, embracing a polypharmacological strategy, has emerged as a promising direction for the development of future therapies. In this review, we propose the concept of NecroFerrins, a class of small molecules that simultaneously inhibit necroptosis and ferroptosis. Within this class, we identify RIPROStatins as a distinct subclass of RIPK1 inhibitors that additionally possess radical-trapping antioxidant activity. The objective of this review is also to stimulate translational research on complex diseases using polypharmacological drugs acting as necrosis inhibitors.

Keywords: Polypharmacology, ferroptosis, necroptosis, NecroFerrins, RIPROStatins

1. Introduction

Cells can die through either accidental cell death (ACD) or regulated cell death (RCD). ACD results from abrupt and severe physical, mechanical, or chemical insults and proceeds independently of regulated molecular pathways. In contrast, RCD is executed through one of a plethora of well-orchestrated signaling networks and defined macromolecular effectors, giving rise to specific biochemical, functional, and immunological consequences^[1]. The controlled elimination of cells constitutes a core biological process that supports proper development and long-term homeostasis in multicellular organisms. The number of RCD pathways has expanded since the first definition of apoptosis in 1972^[2,3], to introduce recognized neologisms for multiple subroutines, including notably pyroptosis, parthanatos, NETotic cell death, necroptosis, and ferroptosis. Cell death classification has been periodically refined by the Nomenclature Committee on Cell Death (NCCD). The NCCD has established authoritative guidelines on the definition and interpretation of cell death since 2005, as summarized in successive position papers, including the 2018 update on molecular mechanisms^[4]. Extensive research has revealed that defective control of individual or combined cell death programs, including regulated necrosis, contributes to the development of an expanding spectrum of human pathologies, including degenerative disorders, inflammatory diseases, and cancer^[5-7]. Because RCD pathways encompass both tightly regulated signaling cascades and processes driven by metabolic instability, they constitute attractive and inherently druggable targets, a prerequisite for the development of effective therapies.

Over the past two decades, major conceptual milestones have shaped our understanding of RCD, marked by the identification of distinct, non-apoptotic cell death modalities. This paradigm shift has led to the identification of several distinct forms of regulated necrosis and inflammatory or metabolic cell death, among which necroptosis and ferroptosis have emerged as particularly



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well-characterized and widely studied examples. For example, in 2005, a major milestone was reached with the characterization of necroptosis as a regulated form of necrosis. Necroptosis is a regulated, caspase-independent form of non-apoptotic cell death driven by a kinase-dependent signaling cascade involving receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and the pseudokinase mixed lineage kinase domain-like pseudokinase (MLKL). Necroptosis can be blocked by RIPK1 inhibitors such as necrostatin-1 (Nec-1)^[8,9]. In 2012, the identification of ferroptosis further expanded the RCD landscape. Ferroptosis is an iron-catalyzed form of regulated necrosis, defined by the accumulation of lipid peroxides, particularly oxidized (phospho)lipids; these arise from an imbalance between lipid peroxidation and cellular antioxidant defenses. Ferroptosis can be blocked by lipophilic radical-trapping antioxidants (RTAs) such as ferrostatins and liproxstatins^[10-12]. Rather than being governed by a single linear signaling cascade, ferroptosis occurs due to the disruption of several metabolic and stress-response pathways, notably iron and lipid metabolism, redox balance, mevalonate signaling, transsulfuration processes, heat-shock protein activation, glutamate/cystine transport, and glutathione (GSH) production^[13].

Although RCD pathways are each driven by distinct molecular and cellular mechanisms, accumulating genetic and biochemical evidence points to substantial plasticity and extensive crosstalk among them^[14,15]. As an example, retinal ischemia-reperfusion injury (IRI) involves the concurrent activation of multiple regulated necrosis pathways, supporting the need for multi-target therapeutic strategies rather than single-pathway interventions^[16]. Historically framed as the “magic bullet” concept by Paul Ehrlich over a century ago, the one-target-one-drug paradigm eventually revealed inherent limitations in treating complex, multifactorial diseases. This limitation drives the emergence of polypharmacological approaches^[17]. Polypharmacology is a novel approach to drug design and therapeutic intervention^[18-20]. As described by the National Library of Medicine in 2014, this emerging approach refers to the development or application of pharmaceutical compounds that simultaneously modulate multiple targets or disease-related pathways^[21]. These may include interactions with distinct protein targets as well as non-protein-centric mechanisms rooted in chemical reactivity, metabolic regulation, or redox control. Among recent approvals of drugs for human use, a significant fraction can be classified as polypharmacological drugs. For instance, Ryszkiewicz *et al.* reported that 18 out of the 73 drugs introduced in Germany between 2023 and 2024 exhibited multi-target pharmacological profiles^[22]. Such multifaceted agents are particularly well-suited to modulating the complex pathological networks underlying multifactorial diseases such as Alzheimer’s disease^[23,24], which are not effectively combatted with single-target therapeutic strategies.

In a recent perspective article published in *Ferroptosis and Oxidative Stress*^[15], Feinsod and Stockwell summarized the extent of crosstalk between ferroptosis and other RCD modalities. The authors notably raised the question of whether necroptosis and ferroptosis could be simultaneously targeted to develop therapies with enhanced efficacy. To address this important question, this review brings together small-molecule compounds reported to simultaneously inhibit necroptosis and ferroptosis and proposes the term **NecroFerrins** for this emerging class of dual inhibitors, together with a classification framework. We further describe the subclass of NecroFerrins, called **RIPROStatins**, which was previously introduced by Delehouzé *et al.*^[25], and refers specifically to RIPK1 inhibitors possessing ROS-scavenging activity.

2. The Druggability of Crosstalk between Necroptosis and Ferroptosis

In pharmacology, druggability refers to the ability of a biological target (usually a protein) to be effectively modulated by a drug-like molecule with enough specificity and potency to produce a therapeutic effect^[26]. Notably, drug-like compounds can be used to modulate druggable biological pathways, as in phenotypic drug discovery, even when the precise molecular target is not yet identified. In cell biology, molecular crosstalk refers to direct mechanistic interactions between distinct RCD pathways that allow signals in one cascade to modulate another, often through shared mediators or feedback loops^[27,28]. Rather than acting independently, mechanisms such as lipid peroxidation, reactive oxygen species (ROS) signaling, and kinase activation can propagate across death programs, integrating multiple cellular stress responses into a unified fate decision. Recent advances have revealed extensive interactions among distinct forms of RCD, demonstrating that activation of one pathway can either enhance or suppress another. These findings offer important mechanistic insights and open new therapeutic avenues for the treatment of complex and refractory diseases^[29]. Also, crosstalk between pathways provides the possibility of targeting drugs to the nodes of intersection. A well-established example of molecular crosstalk is the convergence of pyroptotic, apoptotic, and necroptotic pathways during cellular responses to infection; here, coordinated signaling between these mechanisms culminates in the integrated cell death program termed PANoptosis^[30,31].

Similarly, a growing body of work highlights functional crosstalk between necroptosis and ferroptosis, despite their distinct molecular mechanisms (Figure 1). Necroptosis is driven by RIPK1/RIPK3/MLKL kinase signaling that culminates in mechanical rupture of the plasma membrane^[4], whereas ferroptosis results from iron-dependent peroxidation of PUFA-containing phospholipids, following the failure of antioxidant systems such as glutathione peroxidase 4 (GPX4) and ferroptosis suppressor protein 1 (FSP1)^[32,33]. Despite having distinct mechanisms of initiation, that is, kinase-mediated signaling in necroptosis versus iron-catalyzed lipid peroxidation in ferroptosis, these pathways share common regulatory features. Redox imbalance and accumulation of ROS can amplify both processes, while the molecular chaperone HSP90 contributes to the stability and activity of key signaling components involved in both regulated necrotic pathways^[34,35]. In necroptosis, HSP90 has been reported to regulate the stability and activation of

RIPK1, RIPK3, and MLKL^[35]. In ferroptosis, HSP90 has been reported to promote ferroptotic cell death by facilitating chaperone-mediated autophagy (CMA)-dependent degradation of GPX4^[36]. Ultimately, the necroptosis and ferroptosis pathways converge with the loss of plasma membrane integrity, highlighting membrane vulnerability and redox dysregulation as shared determinants of cell fate and potential therapeutic intervention points. Additional regulators have also been described. In particular, activation of nuclear factor erythroid-derived 2-like protein (NRF2), a key regulator of the antioxidant response, has been reported to reduce the expression of markers of both necroptosis and ferroptosis, and may therefore be considered a key participant in signaling crosstalk^[37]. To date, the fine-tuning of the interplay between necroptosis and ferroptosis remains largely unknown^[15].

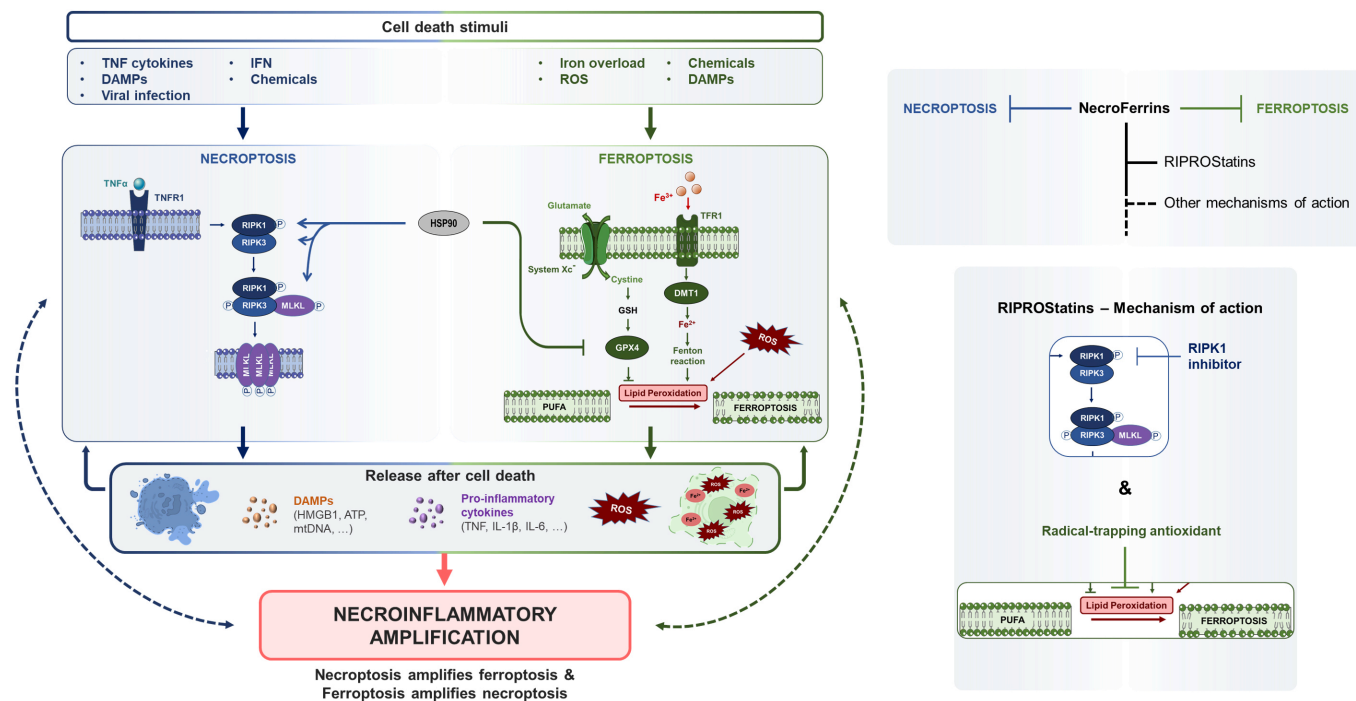


Figure 1. Necroptosis and ferroptosis: converging pathways and dual inhibition. Necroptosis is a kinase-driven, inflammatory form of regulated necrosis mediated by the RIPK1/RIPK3/MLKL signaling axis. Following stimulation by TNF cytokines, DAMPs, viral infection, or chemical stress, RIPK1 and RIPK3 assemble the necrosome, leading to phosphorylation and oligomerization of MLKL. Activated MLKL translocates to the plasma membrane, where it disrupts membrane integrity and promotes necro-inflammatory release of intracellular DAMPs. Ferroptosis is a regulated necrotic cell death driven by iron-dependent lipid peroxidation. Accumulation of intracellular Fe²⁺ and ROS promotes peroxidation of PUFA-containing phospholipids when antioxidant defense systems centered on GPX4 and FSP1 fail. The resulting lipid peroxide accumulation destabilizes cellular membranes and ultimately triggers catastrophic membrane damage. Redox imbalance and increased levels of ROS can potentiate both necroptotic and ferroptotic processes. In addition, the molecular chaperone HSP90 modulates these pathways, for example by facilitating chaperone-mediated autophagic degradation of GPX4 during ferroptosis. The dual inhibitory activity of NecroFerrins and the mechanism of action of RIPROStatins are schematically illustrated in the two boxes on the right side of the figure. Adapted from Servier Medical Art (<https://smart.servier.com>), licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>). DAMPs: damage-associated molecular patterns; ROS: reactive oxygen species; PUFA: polyunsaturated fatty acid; RIPK: receptor-interacting protein kinase; MLKL: mixed lineage kinase domain-like pseudokinase; TNF: tumor necrosis factor; GPX4: glutathione peroxidase 4; FSP1: ferroptosis suppressor protein 1.

Although the identification of shared regulators, such as HSP90^[38] and NRF2^[39], has considerably improved our understanding of the molecular crosstalk between necroptosis and ferroptosis, these proteins are not necessarily optimal therapeutic targets. Most function as pleiotropic signaling hubs involved in numerous vital physiological processes other than RCD. Consequently, their pharmacological modulation may result in broad biological effects and limited therapeutic use due to their toxic effects on other cellular functions.

An alternative approach has emerged, namely, the development of compounds that operate via a distinct pharmacological principle, polypharmacology. Rather than targeting common upstream regulators, these molecules combine, within a single chemical entity, activities directed against the canonical execution machinery of both necroptosis and ferroptosis. Since increasing evidence indicates that these two forms of RCD frequently coexist or are sequentially activated in numerous pathological conditions, targeting a single upstream regulator may not be sufficient to fully prevent tissue injury^[40]. Polypharmacology aims to simultaneously modulate multiple RCD pathways and may provide broader and more robust cytoprotection than approaches directed at a single pathway alone^[25]. The following sections review these polypharmacological compounds, capable of simultaneously inhibiting necroptosis and ferroptosis, and collectively referred to here as NecroFerrins, with emphasis on their mechanisms of action and therapeutic potential.

3. Dual inhibition of Necroptosis and Ferroptosis by NecroFerrins

Ferroptosis is tightly integrated with cellular metabolism, which can be perturbed by the activation of other RCD pathways^[15,41-43]. Consequently, inhibition of ferroptosis may represent a particularly attractive entry point for polypharmacological strategies that target multiple RCD programs. This review focuses exclusively on the dual inhibition of necroptosis and ferroptosis by NecroFerrins, which will provide a complementary mode of inhibition and should represent an emerging class of therapeutic agents for complex diseases. Dual-target compounds ensure simultaneous exposure of both pharmacological activities within the same cells and tissues, may reduce concerns related to drug-drug interactions, and may reduce the likelihood that inhibition of one death pathway is circumvented by compensatory activation of the other. Moreover, from a translational perspective, the development of a single molecular entity with multiple targets may offer advantages over combination therapies, including potentially simplified drug development and regulatory considerations^[20].

3.1 From cell lines to chemical triggers: Tools enabling the discovery of NecroFerrins

The identification of NecroFerrins has been enabled by two decades of methodological advances spanning cell biology, chemical biology, and systems-level profiling. A workflow illustrating putative strategies for NecroFerrin discovery is presented in [Figure 2](#). This figure is further supported by [Table 1](#) and provides representative examples of the cell lines and chemical inducers used in the identification of NecroFerrins. For necroptosis, cell-based assays have been performed across multiple cellular models, including Jurkat FADD-deficient, L929, HT-29, NIH/3T3, MEF, HBMEC, U937, HT22, and 661W cells. In these cell lines, cell death is typically stimulated using well-established inducers such as TNF α , alone or in combination with the pan-caspase inhibitor zVAD-fmk and/or SMAC mimetics (e.g., birinapant, BV-6, SM-164). Mechanistic and target engagement studies rely on RIPK1 kinase activity and binding assays, cellular thermal shift assays (CETSA) for RIPK1 stabilization, and the analysis of the phosphorylation status of RIPK1, RIPK3, and MLKL.

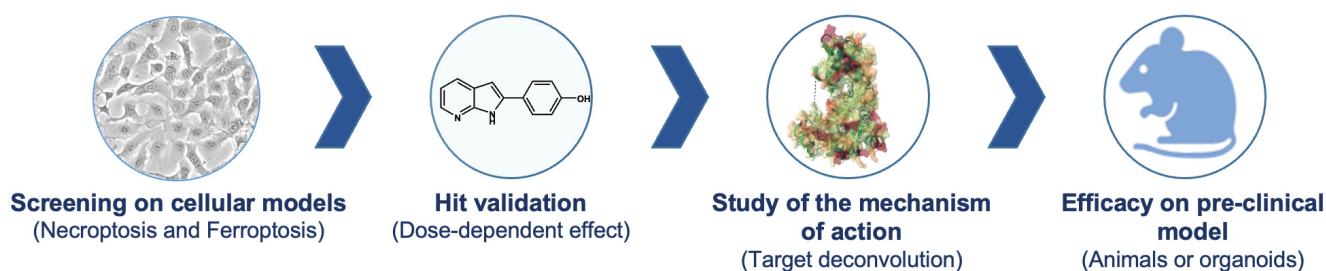


Figure 2. Schematic representation of a *hit-to-lead* workflow used to identify dual inhibitors targeting both necroptosis and ferroptosis pathways.

Table 1. Cell-based and mechanistic assays employed to characterize NecroFerrins.

Necroptosis assays			Ferroptosis assays		
Cell viability/phenotypic assays		Target-based and mechanistic assays	Cell viability/phenotypic assays		Target-based and mechanistic assays
Cell lines	Inducers		Cell lines	Inducers (Class of FIN, I, II, III or IV)	
Jurkat Fadd _{def} ^[8,36,50,71,72]	TNF α	• RIPK1 kinase assay • RIPK1 binding assay • CETSA RIPK1 • RIPK1/RIPK3/MLKL phosphorylation	HT22 ^[25,36,72]	Erastin (I)	• Lipid peroxidation detection (C11-BODIPY (581/591)/MDA/4-HNE) • RTA activity: FENIX assay • mRNA quantification: <i>PTGS2</i>, <i>CHAC1</i>, <i>HMOX1</i> • Iron chelation assay • FerroOrange assay • GSH level quantification • Antioxidant assays (DPPH scavenging activity, H₂DCFDA, MitoSOX)
L929 ^[8,48,67-69]	TNF α + zVAD-fmk		SH-SY5Y ^[25,72]	Glutamate (I)	
HT-29 ^[36,59,67-69]	TNF α + zVAD-fmk		HT-1080 ^[25,36,59,66,67,70]	BSO (I)	
NIH/3T3 ^[25,59]	+ smac mimetic*		NIH/3T3 ^[25,59]	RSL3 (II)	
MEF ^[67,70]			MEF ^[67,70]	FIN56 (III)	
HBMEC ^[65]			Pfa1 ^[25,48,62]	FINO ₂ (IV)	
U937 ^[8,69]			Hepa 1-6 ^[100]		
HT22 ^[36]			786-O ^[68]		
661W ^[36]			HT-29 ^[67,70]		
			A375 ^[68]		
			HK-2 ^[48,68,70]		
			Huh7 ^[68]		
			HepG2 ^[70]		

H1299^[70]
LLC-PK1^[72]
661W^[36]

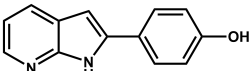
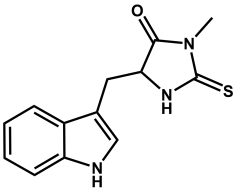
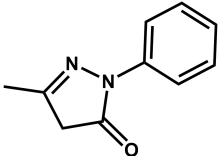
This table summarizes the experimental models used in the original studies to characterize the reported NecroFerrins rather than providing an exhaustive list of available cellular models. Cell lines: Jurkat Fadd_{def}, human lymphocytes with FADD deficiency; SH-SY5Y, human neuroblastoma cell line; Pfa1, mouse embryonic fibroblast cell line; HBMEC, human brain microvascular endothelial cells; Hepa 1-6, mouse hepatocellular carcinoma cell line; HT-29, human colorectal adenocarcinoma cell line; NIH/3T3, mouse embryonic fibroblast cell line; HT-1080, human fibrosarcoma cell line; MEF, mouse embryonic fibroblast cell line; L929, mouse fibroblast cell line; A375, human melanoma cell line; U937, human myeloid leukemia cell line; HT22, mouse hippocampal neuronal cell line; 661W, murine cone photoreceptor-derived cell line; 786-O, human renal adenocarcinoma cell line; HK-2, human proximal tubular epithelial cell line; Huh7, human hepatocellular carcinoma cell line; HepG2, human hepatocellular carcinoma cell line; H1299, human non-small cell lung carcinoma cell line; LLC-PK1, porcine renal epithelial cell line. Classes of FINs: Class I, Block the system Xc⁻ antiporter, thereby reducing cystine uptake; Class II, Inhibit GPX4; Class III, Promote GPX4 degradation, target squalene synthase, and reduce cellular CoQ10 antioxidant levels; Class IV, Oxidize ferrous iron and lipidome, leading to indirect GPX4 inactivation. *: *Birinapant*, *BV-6*, *SM-164*; FIN: ferroptosis inducer; TNF: tumor necrosis factor; RIPK: receptor-interacting protein kinase; MLKL: mixed lineage kinase domain-like pseudokinase; CETSA: cellular thermal shift assay; RSL3: (1S,3R)-Ras-selective lethal small molecule 3; BSO: buthionine sulfoximine; RTA: radical-trapping antioxidant; MDA: malondialdehyde; 4-HNE: 4-hydroxynonenal; FENIX: fluorescence-enabled inhibited autoxidation; PTGS2: prostaglandin-endoperoxide synthase 2; CHAC1: ChaC glutathione-specific γ-glutamylcyclotransferase 1; HMOX1: heme oxygenase 1; GSH: glutathione; DPPH: 2,2-diphenyl-1-picrylhydrazyl; H2DCFDA: 2',7'-dichlorodihydrofluorescein diacetate.

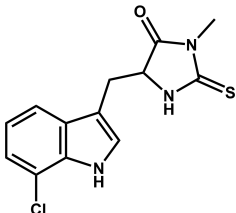
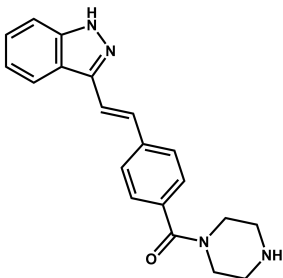
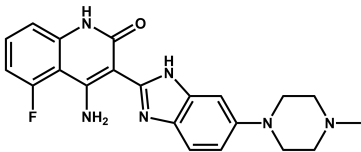
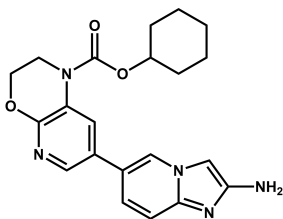
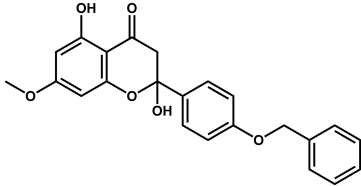
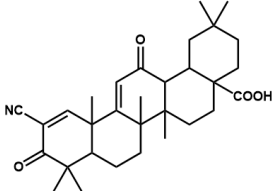
For ferroptosis, cell-based assays have been conducted in a broad panel of cell lines, including HT22, SH-SY5Y, HT-1080, NIH/3T3, MEF, Pfa1, Hepa1-6, 786-O, HT-29, A375, HK-2, Huh7, HepG2, H1299, LLC-PK1, and 661W cells. Cell lines are exposed to canonical ferroptosis inducers representing the four classes (I to IV) of ferroptosis-inducing agents (FINs), such as erastin (I), glutamate (I), RSL3 (II), FIN56 (III), and FINO2 (IV). This classification is based on the distinct mechanisms by which ferroptosis is induced, as described by Li *et al.*^[44]. Ferroptosis-associated endpoints include the assessment of lipid peroxidation (e.g., C11-BODIPY (581/591), malondialdehyde, and 4-hydroxynonenal), evaluation of RTA activity (e.g., fluorescence-enabled inhibited autoxidation (FENIX) assay), and gene expression analysis of ferroptosis markers (e.g., PTGS2, CHAC1, HMOX1). Additional readouts include intracellular iron quantification (e.g., FerroOrange), GSH level determination, and general oxidative stress measurements using probes such as H2DCFDA and MitoSOX.

While markers of necroptosis are now well established, particularly the assessment of MLKL phosphorylation, significant variability persists in the assays used to characterize ferroptosis. To address this issue, Mishima *et al.* have provided guidelines for the rigorous identification and validation of ferroptosis and its inhibitors^[45]. Together, these complementary cellular and biochemical approaches provide a framework for the identification and characterization of dual inhibitors targeting both necroptosis and ferroptosis.

To date, these approaches have enabled the identification of nine molecules that have been shown to inhibit both necroptosis and ferroptosis (Table 2). Table 3 presents their classification into NecroFerrins, including two members of the RIPROStatin subclass.

Table 2. Small-molecule inhibitors of necroptosis and ferroptosis described so far in the literature.

Molecule	Chemical structure (MW in g/mol)	Effect on Necroptosis	Effect on Ferroptosis	Ref.
Sibiriline	 (210.23)	• EC₅₀ Jurkat Fadd_{def} (TNFα) = 1.2 μM • IC₅₀ RIPK1 = 1.03 μM • Kd RIPK1 = 218 nM	• EC₅₀ SH-SY5Y (RSL3) = 1.13 μM • RTA K_{inh} liposomes = 10³ M⁻¹ s⁻¹	[25,50]
Nec-1	 (259.33)	• EC₅₀ Jurkat fadd_{def} (TNFα) = 0.49 μM • IC₅₀ RIPK1 = 2.01 μM • Kd RIPK1 = 31 nM	• Protects Pfa1 cells from erastin, RSL3 and BSO-induced cell death (EC₅₀ ≈ 1-10 μM) • Radical scavenging activity IC₅₀ = 90 μM (DPPH) • RTA activity > 20 μM	[8,48,50,62,72,101]
Edaravone	 (174.2)	• Decreases pS166-RIPK1 signal after TSZ-induced cell death in HBMEC cells (observed by WB; concentration not indicated)	• Protects Hepa 1-6 cells from RSL3 and erastin-induced cell death at 50 and 100 μM • Radical scavenging activity IC₅₀ = 53.4 μM (DPPH) • Lipid peroxidation inhibition: IC₅₀ = 22.79 μM (MDA assay)	[65,66,100]

		• Reduces lipid ROS at 100 μM (Bodipy C11/4-HNE)	
Nec-1f	 (293.77)	• Protects HT-29 and NIH/3T3 cells from TSZ-induced cell death (at 10 μM) • Decreases pS166-RIPK1 signal (WB) after TSZ-induced cell death in HT-29 cells (at 10 μM)	• Protects HT-1080 and NIH/3T3 cells from erastin and RSL3-induced cell death (at 30 μM) • No activity detected using liposomes co-oxidation assay [59]
KW-2449	 (332.41)	• Protects HT-29 and U937 cells from TSZ-induced cell death (≥ 0.1 μM) • Decreases pS166-RIPK1 signal (WB) after TSZ-induced cell death in HT-29 cells (at 0.5 μM) • Kd RIPK1 = 100 nM	• EC_{50} MEF (RSL3) = 0.169 μM • Protects HT-1080, HT-29, MEF cells from erastin and RSL3-induced cell death (at 1 μM) • Reduces lipid ROS at 1 μM (Bodipy) • No radical scavenging activity (DPPH) [69,70]
Dovitinib	 (392.44)	• EC_{50} L929 (TZ) = 0.361 μM • Inhibits RIPK1 activity at 10 μM • Decreases pS166-RIPK1 signal (WB) after TSZ-induced cell death in HT-29 cells (at 5 μM)	• EC_{50} A375 (RSL3) = 0.337 μM • Reduces lipid ROS at 5 μM (Bodipy) • No radical scavenging activity (DPPH) [68]
Zharp1-163	 (393.45)	• EC_{50} HT-29 (TSZ) = 0.1 μM • IC_{50} RIPK1 = 0.406 μM • Kd RIPK1 = 240 nM	• EC_{50} MEF (RSL3) = 1.39 μM • Reduces lipid ROS at 10 μM • No radical scavenging activity (DPPH) [67]
Nigratine (6E11)	 (392.41)	• EC_{50} Jurkat fadd_{def} ($\text{TNF}\alpha$) = 4.6 μM • IC_{50} RIPK1 = 1.6 μM • Kd RIPK1 = 130 nM	• EC_{50} SH-SY5Y (RSL3) = 6.89 μM • Reduces lipid ROS at 10 μM (Bodipy) • Weak radical scavenging activity (DPPH) [71,72]
CDDO (bardoxolone)	 (491.67)	• EC_{50} HT22 (TSZ) = 10 μM • Decreases pS166-RIPK1 signal (WB) after TSZ-induced cell death in HT22 cells (at 10 μM) • No inhibition of RIPK1 kinase activity <i>in vitro</i>	• EC_{50} HT22 (glutamate) = 5.5 μM • Reduces lipid ROS at 10 μM (MDA assay) • No radical scavenging activity (DPPH) [36]

For each compound, the chemical structure and key supporting experimental evidence are reported. Necroptosis-related data include effects on cell death and RIPK1 signaling or kinase activity. Ferroptosis-related data include effects on ferroptotic cell death and lipid peroxidation (lipid ROS). Representative references supporting these findings are provided. For instances in which multiple cell-based assays, cell lines, or death inducers have been described in the cited references, only the most representative or most effective results are included in this table. TZ: $\text{TNF}\alpha$ + zVAD-fmk; TSZ: $\text{TNF}\alpha$ + zVAD-fmk + smac mimetic (birinapant, BV-6, SM-164); RSL3: (1S,3R)-Ras-selective lethal small molecule 3; MDA: malondialdehyde; 4-HNE: 4-hydroxynonenal; DPPH: 2,2-diphenyl-1-picrylhydrazyl; WB: Western-blot.

Table 3. Classification of NecroFerrins. Molecules that fulfill the criteria described in **Box 1** are classified as members of the RIPROStatin subclass. * For edaravone and Nec-1f, we recommend performing a kinase assay to confirm their inhibitory activity against RIPK1.

Molecule	Necroptosis cellular assay	Ferroptosis cellular assay	RIPK1 inhibition demonstrated	RTA demonstrated	NecroFerrin	RIPROStatin
Sibiriline	✓	✓	✓	✓	✓	✓
Nec-1	✓	✓	✓	✓	✓	✓
Edaravone	✓	✓	✓*	Unknown	✓	To be validated
Nec-1f	✓	✓	✓*	×	✓	No
KW-2449	✓	✓	✓	Unknown	✓	No
Dovitinib	✓	✓	✓	Unknown	✓	No
Zharp1-163	✓	✓	✓	Unknown	✓	No
Nigratine	✓	✓	✓	Unknown	✓	No
CDDO	✓	✓	×	Unknown	✓	No

A compound is classified as a NecroFerrin when experimental evidence demonstrates inhibition of both necroptosis and ferroptosis in pathway-specific cellular assays. RIPROStatins are a subclass of NecroFerrins that additionally exhibit both RIPK1 inhibitory activity and RTA activity. An entry of “Unknown” indicates that the corresponding data have not yet been reported. The symbols (✓) and (×) indicate that the compound was tested experimentally and showed positive or negative activity, respectively. RTA: radical-trapping antioxidant; RIPK: receptor-interacting protein kinase; CDDO: 2-amino-5-chloro-N,3-dimethylbenzamide.

3.2 RIPROStatin - a subclass of potent NecroFerrins

The development of dual inhibitors targeting actors involved in necroptosis and ferroptosis may utilize either a multi-target directed ligand strategy alone, or a combinatorial strategy that integrates target-based and mechanism-based inhibitors. The activity of mechanism-based inhibitors (also known as chemistry-based inhibitors) is determined by their chemical reactivity (e.g., radical-trapping antioxidants, RTAs^[46]) rather than by binding to a single macromolecular target. By analogy, target-based inhibitors can be viewed as key-lock pairs, that is, an inhibitor bound to a specific molecular target, whereas mechanism-based inhibitors such as RTAs resemble fire extinguishers, neutralizing a broad reactive threat (i.e., radicals) throughout the cell.

Ferroptosis is characterized by lethal lipid peroxidation, a feature that underlies the efficacy of radical-trapping antioxidants such as the pioneering inhibitors ferrostatin-1 (Fer-1) and liproxstatin-1, reported by the Stockwell and Conrad groups, respectively^[10,47,48]. In contrast, necroptosis is driven by kinase signaling, and the development of RIPK1 inhibitors represents the most widely recognized therapeutic strategy. Nec-1 was the first inhibitor of necroptosis^[8] and was later shown to act by inhibiting the activity of RIPK1^[49]. The identification of these two RCD pathways highlights the importance of chemical probes in uncovering novel molecular pathways and elucidating their regulation.

The concept of RIPROStatins, RIPK1 inhibitors that also possess ROS-scavenging activity, is closely linked to two mechanisms of action: RTA activity and kinase inhibition (Figure 1). Indeed, if a RIPK1 kinase inhibitor also exhibits RTA activity, it is expected to inhibit both ferroptosis and necroptosis. This concept was exemplified by the discovery of a 7-azaindole derivative, the 4-(1H-pyrrolo[2,3-b]pyridin-2-yl)phenol compound^[50], also known as sibiriline.

Sibiriline is a first-in-class example of a mechanistically integrated dual inhibitor. Sibiriline was shown to inhibit necroptosis in various cell lines, including FADD-deficient Jurkat lymphocyte cells, with an EC₅₀ value of 1.2 μM. Mechanistic analysis demonstrated that inhibition of RIPK1, with an IC₅₀ value of 1.03 μM, likely explains the suppression of the necroptosis pathway^[50]. Moreover, sibiriline was also shown to inhibit ferroptosis in a variety of cell lines triggered by various classes of ferroptosis inducers, with EC₅₀ values in the micromolar range (e.g., in HT1080 human fibrosarcoma cells treated with RSL3, a covalent inhibitor of GPX4). The inhibition of ferroptosis was attributed to the suppression of lipid peroxidation through the trapping of phospholipid-derived peroxyl radicals, consistent with its RTA activity^[25]. Based on the guidelines outlined in **Box 1** and on the criteria summarized in Figure 3, sibiriline is therefore classified as a member of the RIPROStatin subclass of cell-death inhibitors. Its efficacy has also been demonstrated in several disease-related models. In mice, sibiriline demonstrated a protective effect in immune-mediated acute hepatitis, which was associated with significantly reduced serum aspartate aminotransferase and alanine aminotransferase levels and attenuated liver injury^[50]. *In vitro*, sibiriline also showed dose-dependent protection against cell death in cell-based models of Parkinson's disease and cystic fibrosis^[25]. Next, methods were developed to investigate sibiriline's *in vivo* metabolic fate and to

support its preclinical research^[51].

Box 1: Which state-of-the-art assays are required to classify a dual ferroptosis–necroptosis inhibitor (NecroFerrin) as a RIPROStatin?

First, the compound of interest should demonstrate inhibition of both necroptosis and ferroptosis in pathway-specific cell-based assays, with protection confirmed by cell viability and/or cytotoxicity measurements^[45,52,53]. Well-characterized inhibitors of necroptosis and ferroptosis, such as Nec-1s and Fer-1, respectively, must be used to validate experimental data.

On the necroptosis side, inhibition of RIPK1 kinase activity should be demonstrated using a range of *in vitro* assays, including the ADP-Glo™ kinase assay (Promega, Madison, WI, USA)^[54–56]. Although these functional biochemical assays are effective, they generally require substantial amounts of active enzymes to generate robust signals. The production and purification of active recombinant RIPK1 kinase from Sf9 insect cells were described by Maki *et al.* in 2013^[57]. Alternatively, when recombinant RIPK1 production and purification are not feasible, detection of RIPK1 Ser166 autophosphorylation by immunoblotting can be performed on crude extracts from cells or tissues treated with the inhibitor of interest, in order to assess inhibition of RIPK1-dependent necrotic signaling^[58,59]. Target-engagement assays, such as NanoBRET®-based assays (Promega) or the CETSA, can also be used to monitor compound binding to RIPK1 in a cellular context^[54,60].

On the ferroptosis side, RTA activity should be demonstrated using the FENIX-1 and -2 (Fluorescence-Enabled Inhibited Autoxidation) assays, developed by the Derek Pratt group^[61,62]. The FENIX assays are recognized methods for assessing the activity of lipophilic RTAs in liposome systems that mimic cellular phospholipid membranes, thereby providing relevant models for studying lipid peroxidation associated with ferroptosis^[45,64]. It is important to note that, although antioxidant properties are often assessed using the DPPH reduction assay, experimental results have shown that this method does not reliably predict either the RTA activity or the ferroptosis-inhibiting activity of the compounds^[61]. The criteria used to classify compounds as NecroFerrins or RIPROStatins are summarized in the decision tree depicted in Figure 3.

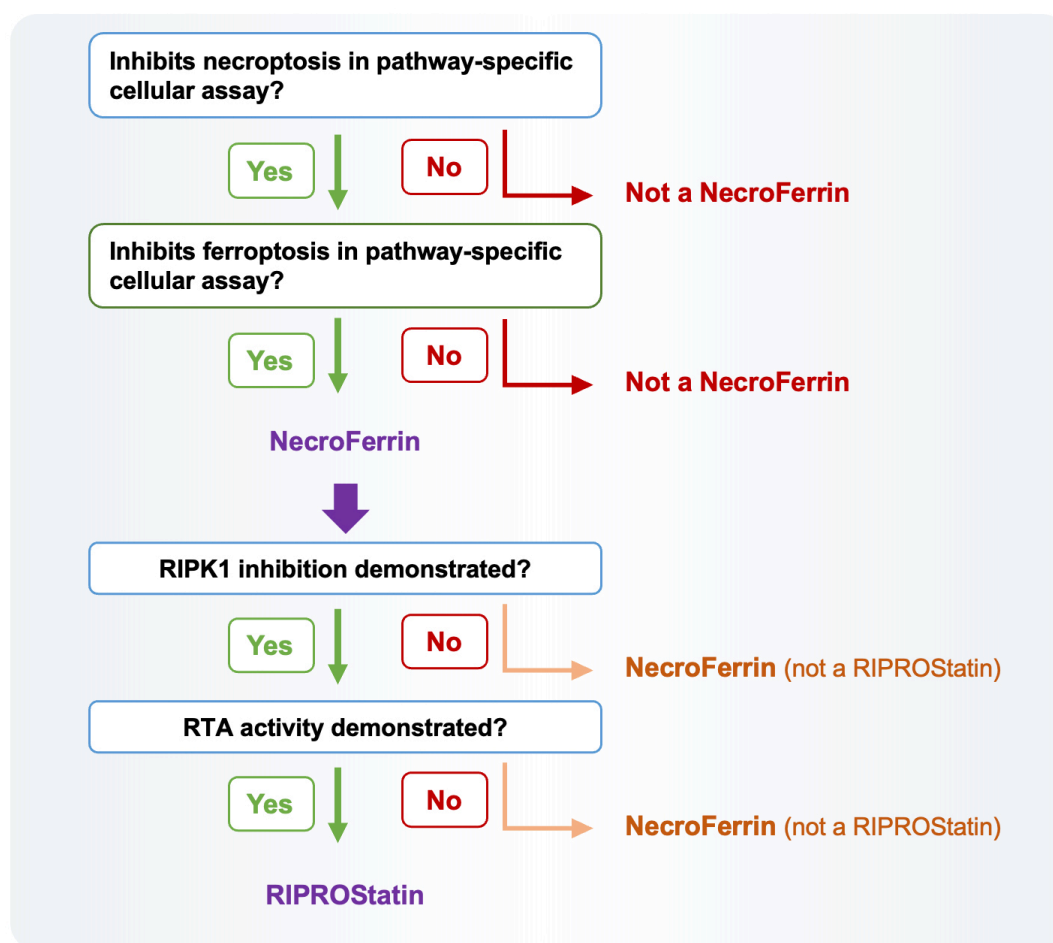


Figure 3. Decision tree illustrating the classification of compounds as NecroFerrins and RIPROStatins according to the methodological criteria detailed in Box 1. RIPK: receptor-interacting protein kinase; RTA: radical-trapping antioxidant.

As indicated in [Table 2](#) and [Table 3](#), the prototypical inhibitor of necroptosis, Nec-1, can also be included in the RIPROStatin subclass. Indeed, Friedmann Angeli *et al.*^[48] demonstrated that Nec-1 abrogates cell death induced by the GPX4 inhibitor RSL3 (1 μ M) in Pfa-1 mouse fibroblasts in a dose-dependent manner. Subsequently, Mallais *et al.*^[62] showed that Nec-1 does not possess intrinsic RTA activity but can be activated in cells in the presence of hydroperoxides, thus functioning as an RTA and suppressing ferroptosis. Interestingly, the ferroptosis-inhibitory activity of Nec-1 was initially described as an “off-target” effect. More recently, Derek A. Pratt and co-workers provided further mechanistic support for the proposed anti-ferroptotic activity of Nec-1 and identified new necrostatin derivatives with enhanced ferroptosis inhibition while retaining anti-necroptotic activity, further validating Nec-1 as a prototype dual inhibitor of necroptosis and ferroptosis^[63].

Apart from sibiriline and Nec-1, edaravone could provisionally be classified as a RIPROStatin as defined by the criteria listed in **Box 1**. Edaravone is a free radical scavenger developed by Mitsubishi Tanabe Pharma Corporation and marketed as Radicava®, which was approved by the US Food and Drug Administration in 2017 for the treatment of amyotrophic lateral sclerosis. Originally designed as a potent antioxidant, edaravone mitigates oxidative stress by scavenging ROS, including hydroxyl radicals, lipid peroxy radicals, and peroxynitrite, and has also been reported to modulate ferroptotic processes^[64]. Subsequent studies further demonstrated that edaravone can inhibit RIPK1-RIPK3-MLKL-mediated necroptosis^[65]. As indicated in [Table 2](#) and [Table 3](#), additional liposome-based FENIX assays, as well as a direct evaluation of the RIPK1 inhibitory activity of edaravone (e.g., using a kinase assay), are still required to fully validate its classification as a RIPROStatin.

It is worth noting that an edaravone-based hybrid molecule, compound 23a (Cpd 23a, also known as RIPK1-IN-33), was subsequently developed. This molecule comprises two functional domains designed to simultaneously target necroptosis, ferroptosis, and oxidative stress^[66]. Nevertheless, the currently available evidence is insufficient to classify Cpd 23a as a NecroFerrin. Although it has been evaluated in a ferroptosis cell-based assay, the study assessed only PTGS2 transcription without measuring cell viability, and no cell-based evidence of necroptosis inhibition has been reported. We therefore consider the available data too preliminary to support its classification as a NecroFerrin.

3.3 Alternative strategies for dual targeting of necroptosis and ferroptosis

As noted in [Table 2](#) and [Table 3](#), a subset of six other compounds, Nec-1f^[59], Zharp1-163^[67], Dovitinib^[68], KW-2449^[69,70], nigratine^[71,72], and 2-amino-5-chloro-N,3-dimethylbenzamide (CDDO)^[36], has also been described as NecroFerrins. However, based on the criteria defined in **Box 1**, these compounds cannot be classified as RIPROStatins. In most cases, their mechanisms of action for the inhibition of ferroptosis remain only partially characterized, and their dual activity likely arises from indirect or context-dependent effects rather than from a defined combination of RIPK1 inhibition and RTA activity.

Five of the compounds in [Table 2](#) and [Table 3](#) act as necroptosis inhibitors by virtue of their inhibition of RIPK1 kinase: Nec-1f^[59], KW-2449^[69,70], Dovitinib^[68], Zharp1-163^[67], and nigratine^[71,72].

Nec-1f is a close derivative of the original RIPK1 inhibitor Nec-1. This compound retains the ability to inhibit RIPK1 and exhibits weak inhibition of ferroptosis, with effects detected at 30 μ M. As shown in this study, no activity was observed in the liposome co-oxidation assay, indicating that Nec-1f does not function as an RTA^[59]. The molecular target of Nec-1f in the context of ferroptosis remains to be identified.

KW-2449 is a NecroFerrin reported to act as a RIPK1 inhibitor^[69] and also as an autophagy inhibitor; the latter activity may account for its ability to suppress ferroptosis. Studies have suggested that inhibition of ULK1 (Unc-51-like kinase 1) by KW-2449 underlies this effect, highlighting the potential of multi-target kinase inhibitors as NecroFerrins^[70]. Similarly, dovitinib (CHIR-258), a multi-target receptor tyrosine kinase inhibitor initially developed to target Fms-like tyrosine kinase 3^[73], has been reported to inhibit ferroptosis through an additional mechanism of action: this NecroFerrin acts, at least in part, by downregulating the NRF2/HMOX1 pathway. However, given its broad kinase inhibitory profile, NRF2 is unlikely to represent the sole target of dovitinib, and its ferroptosis-inhibitory effects may involve multiple mechanisms^[68]. Further studies are therefore required to fully elucidate the molecular basis of dovitinib-mediated ferroptosis inhibition.

Zharp1-163 was identified as an inhibitor of lipid ROS peroxidation associated with ferroptosis; however, no observable antioxidant activity was detected using a DPPH assay. Identifying its specific target in ferroptosis will be essential to better understand the underlying molecular mechanisms^[67].

Nigratine represents a distinct class of inhibitors, as it is derived from a natural product scaffold belonging to the flavanone family, in contrast to the other fully synthetic compounds. Nigratine is a highly selective RIPK1 inhibitor with nanomolar affinity (Kd); the mechanism underlying its ferroptosis-inhibitory activity is currently under investigation^[71,72]. In this context, affinity-based chemical proteomics and related strategies have emerged as powerful tools to identify intracellular targets and tease out the mechanisms of bioactive small molecules, thereby improving their pharmacological characterization^[74-76].

Interestingly, the 2-amino-5-chloro-N,3-dimethylbenzamide compound (referred to as CDDO in the original study, also known as bardoxolone) stands out among NecroFerrins, because it targets HSP90, a shared upstream regulator involved in both the necroptosis

and ferroptosis pathways^[36]. However, its mechanism of action appears to be indirect; its activity is likely mediated through modulation of HSP90-dependent processes, including (i) activation of RIPK1 and (ii) degradation of GPX4 via the regulation of CMA^[36]. While HSP90 represents an attractive therapeutic target in oncology, due to its role in stabilizing multiple oncogenic client proteins, its inhibition is associated with significant limitations and substantial toxicity that restrict its broader therapeutic application. For instance, the benzoquinone ansamycin, geldanamycin, a well-characterized HSP90 inhibitor, exhibits potent biological activity but also considerable adverse effects that have limited its clinical development^[77]. Altogether, CDDO highlights the potential of targeting regulatory nodes shared between ferroptosis and necroptosis. However, safety concerns associated with HSP90 inhibition remain a major obstacle to the therapeutic development of this class of compounds^[78].

3.4 Evaluation of NecroFerrins in *in vivo* models of human disease

Compounds identified as NecroFerrins have been evaluated in a growing range of *in vivo* disease models, including pathologies in which necroptosis and/or ferroptosis have been implicated (Table 4). These studies collectively demonstrate protective effects in multiple organ systems, including the central nervous system, eye, heart, kidney, liver, and lung, while also suggesting broader applicability to additional pathological contexts in which intertwined RCD pathways are involved.

Table 4. *In vivo* evaluation of NecroFerrins in relevant models of human disease.

Organ	<i>In Vivo</i> Models(Compound Evaluated)	Associated Pathologies	Ref.
CNS	• Spinal cord injury (Edaravone)	• Spinal cord injury	[8,65,66,79-81,102]
	• MCAO (Nec-1 , Edaravone)	• Ischemic brain injury/Ischemic stroke	
	• SAH (Nec-1 , CDDO)	• Early brain injury in SAH	
Eye	• Retinal ischemia reperfusion injury (Nec-1)	• Retinal IR injury	[82,83]
	• Retinal NMDA-excitotoxicity (Nec-1)	• Glaucoma	
Heart	• Cardiac transplantation (Nec-1f)	• Transplantation/IRI	[59,84]
	• Acute myocardial infarction (Nec-1)	• Myocardial infarction	
Kidney	• Bilateral renal ischemia-reperfusion injury (Nec-1f , Zharp1-163 , Nec-1)	• Acute kidney injury (I/R, nephrotoxicity)	[59,67,69,85,86]
	• Cisplatin-induced acute kidney injury (Nec-1f , Zharp1-163 , Nec-1 , KW-2449)		
	• Acute oxalate nephropathy (Nec-1f)		
Liver	• Concanavalin-A induced hepatitis (Sibiriline , Dovitinib)	• Immune-dependent hepatitis	[50,68,87]
	• APAP-induced hepatotoxicity (Nec-1)	• Acute liver failure/acute liver injury	
Lung	• LPS-induced ALI (Nec-1 , Edaravone)	• Acute lung injury (ALI)	[72,88-91]
	• Skin-flap model or IRI (Nec-1)	• Lung IRI	
	• Intestinal I/R-induced lung injury (Edaravone)		
	• TSZ or cumene hydroperoxide-induced cell death (Nigratine)*		
Whole body	• TNF-induced SIRS (Zharp1-163 , Dovitinib)	• SIRS	[67,68,70]
	• Iron-overload-induced MODS (KW-2449)	• MODS	

Overview of organ systems in which dual inhibitors have been tested, including the eye, brain, lungs, heart, liver, and kidney. For each organ, the corresponding *in vivo* models, associated human diseases, and literature references are summarized, highlighting the broad therapeutic potential of targeting regulated necrosis pathways. *: *in vitro* assay performed on airway organoids derived from human healthy lung tissue; CNS: central nervous system; TNF: tumor necrosis factor; MCAO: middle cerebral artery occlusion; SAH: subarachnoid hemorrhage; NMDA: N-methyl-D-aspartate; IRI: ischemia-reperfusion injury; APAP: acetaminophen; LPS: lipopolysaccharide; ALI: acute lung injury; TSZ: TNF α /smac mimetic/zVAD-fmk; SIRS: systemic inflammatory response syndrome; MODS: multiple organ dysfunction syndrome.

In the central nervous system, NecroFerrins such as Nec-1 and edaravone have been shown to reduce tissue damage and improve functional outcomes in models of spinal cord injury, ischemic stroke (the middle cerebral artery occlusion model), and subarachnoid hemorrhage^[8,65,66,79-81]. In ocular models, Nec-1 confers protection against retinal ischemia-reperfusion injury and N-methyl-D-aspartate-induced excitotoxicity, supporting a role in neurodegenerative eye diseases such as glaucoma^[82,83].

Cardioprotective effects of Nec-1 and its derivatives have been reported in cardiac transplantation and myocardial infarction models, in which these compounds limit ischemia-reperfusion injury^[59,84]. Similarly, robust renoprotective effects have been observed in

multiple models of acute kidney injury, including ischemia-reperfusion, cisplatin-induced nephrotoxicity, and oxalate nephropathy, using compounds such as Nec-1f, Zharp1-163, and KW-2449^[59,67,69,85,86].

In the liver, NecroFerrins mitigate both immune-mediated hepatitis (e.g., the Concanavalin A model) and drug-induced liver injury (e.g., acetaminophen overdose), highlighting their relevance in acute liver failure^[50,68,87]. In pulmonary disease, these compounds attenuate acute lung injury induced by lipopolysaccharide, ischemia-reperfusion, or systemic insults; corroborating evidence has been obtained from human airway organoid experiments^[72,88-91].

Finally, systemic administration of NecroFerrins has demonstrated efficacy in whole-body inflammatory conditions, including TNF-induced systemic inflammatory response syndrome and iron overload-induced multiple organ dysfunction syndrome^[67,68,70].

Together, these findings demonstrate that compounds identified as NecroFerrins exhibit protective effects across a broad range of *in vivo* disease models in which necroptosis and/or ferroptosis have been implicated, supporting their therapeutic potential while highlighting the need for further studies to establish the contribution of dual pathway inhibition in individual disease contexts.

4. Perspectives and Conclusions

The identification of the NecroFerrin class of inhibitors has established a pharmacological framework for the simultaneous targeting of necroptosis and ferroptosis, two regulated necrosis pathways that frequently coexist in pathological contexts associated with inflammation and oxidative stress. Accumulating evidence supports the notion that dual inhibition may offer therapeutic benefits in complex diseases in which multiple cell death programs are engaged, leading to a so-called pathological synergy effect^[37]. *In vivo* studies have provided proof of concept, with protective effects reported in various models including neurodegeneration, acute kidney injury, liver injury, and pulmonary disease. Notably, Linkermann *et al.* demonstrated in an IRI model that the combined use of inhibitors of ferroptosis and necroptosis provided significantly greater protection of renal function than monotherapy^[92]. Building on these findings, seven years later, Andreas Linkermann and colleagues reported the characterization of Nec-1f (Table 2), a NecroFerrin combining RIPK1 inhibition with anti-ferroptotic activity. The compound demonstrated promising efficacy in protecting experimental models against ischemia-reperfusion injury^[59]. Our research groups at the Station Biologique de Roscoff and SeaBeLife Biotech (France) have also contributed to the discovery and classification of NecroFerrins. In this context, sibiriline provided significant neuroprotection in a cellular model of Parkinson's disease, supporting the concept that the concurrent inhibition of necroptosis and ferroptosis may represent an effective strategy to promote neuronal survival^[25]. However, the respective contributions of necroptosis and ferroptosis to these pathological outcomes remain incompletely defined. Given the overlapping features of regulated necrosis pathways, the integration of genetic and pharmacological approaches will be essential to better delineate pathway-specific roles *in vivo*.

Several additional considerations should be taken into account when evaluating the translational potential of NecroFerrins. Some compounds discussed in this review, including Dovitinib^[73] and KW-2449^[69], were originally developed as multi-target kinase inhibitors and may therefore exert biological effects beyond RIPK1 inhibition. Consequently, the protective effects observed in experimental models should not be assumed to result exclusively from the simultaneous inhibition of ferroptosis and necroptosis. RCD pathways form a highly interconnected network, and their relative contribution may vary depending on the disease context. Accordingly, further studies will be required to determine the disease settings in which dual inhibition of ferroptosis and necroptosis provides the greatest therapeutic benefit.

While the present review focuses on pharmacological strategies aimed at simultaneously inhibiting ferroptosis and necroptosis, an alternative therapeutic concept involves the opposite approach: small molecules capable of concomitantly activating multiple cell death pathways, including ferroptosis. For example, the multikinase inhibitor sorafenib, a clinically approved anticancer agent, can trigger ferroptosis in addition to apoptosis, partly through inhibition of the cystine transporter SLC7A11^[93]. More recently, the bromo- and extra-terminal bromodomain inhibitor JQ1 and related derivatives have been reported to promote both ferroptotic and apoptotic cell death, suggesting that pharmacological activation of distinct death programs could be exploited for the treatment of aggressive malignancies such as triple-negative breast cancer^[94].

A major challenge for the clinical translation of NecroFerrins lies in the limited availability of specific biomarkers, including tissue and circulating markers, that are capable of capturing the dual or sequential activation of necroptosis and ferroptosis. In the case of ferroptosis, although lipid peroxidation is a central hallmark, it is not exclusive to this process; it may instead be a sequela of broader oxidative stress^[95]. Similarly, commonly used assays lack the specificity required to distinguish ferroptosis from other forms of regulated necrosis in tissues or biofluids. The identification of reliable and selective biomarkers will therefore be critical for monitoring target engagement and for enabling patient stratification.

The limitation related to biomarkers is particularly evident in the evaluation of dual inhibitors. Because ferroptosis and necroptosis can contribute simultaneously to tissue injury, the development of translational biomarker strategies should address readouts for both pathways. Multiparametric approaches combining biomarkers of necroptosis (e.g., p-MLKL)^[96] and ferroptosis (e.g., lipid peroxidation products)^[97] may provide a more informative assessment of disease activity and treatment response than the

measurement of individual biomarkers alone. Complementary functional assays based on damage-associated molecular pattern release could further strengthen the evaluation of dual ferroptosis-necroptosis inhibitors in preclinical and clinical settings^[97,98]. Rather than striving exclusively for pathway-specific markers, an alternative and potentially more informative approach may consist of focusing on integrated functional readouts that reflect disease modulation. Such readouts could include tissue protection, preservation of organ function, reduction of inflammatory responses, or normalization of metabolic and redox imbalances.

Looking ahead, an important next step will be the clinical translation of dual ferroptosis and necroptosis inhibitors, including RIPROStatins and other NecroFerrins. The selection of which pathologies to target, together with the identification of optimal biomarkers, will be crucial. At the same time, continued innovation will be required to discover and optimize new classes of multi-target agents. Beyond target selection itself, future development of NecroFerrins will require overcoming substantial medicinal chemistry challenges related to balancing target engagement, radical-trapping activity, physicochemical properties, tissue exposure, and safety within a single molecular framework. Such multidimensional optimization likely explains why only a limited number of bona fide dual inhibitors have been identified to date. In this context, AI-assisted polypharmacology is poised to transform multi-target drug discovery in the coming decade. By integrating large-scale biological datasets, structure-based modeling, and chemoinformatics, AI-assisted approaches offer unprecedented opportunities to design agents capable of modulating complex cellular pathways such as RCD^[99]. Importantly, these strategies may combine protein-centric targeting with chemically reactive modalities, including radical-trapping activities capable of controlling ferroptosis, to generate innovative therapeutics that act through multiple complementary mechanisms. Such advances could ultimately enable more effective interventions against complex diseases and consequently improve patient outcomes.

In summary, NecroFerrins represent a promising strategy to modulate interconnected cell death pathways. In this context, RIPROStatins constitute a prototypical class of dual inhibitors combining complementary mechanisms of action, and may represent an advanced framework for the development of next-generation cytoprotective therapies. Importantly, the discovery of mechanistically integrated dual inhibitors should not be viewed as a predictable consequence of combining kinase inhibition and antioxidant properties, but rather as the outcome of complex and highly constrained pharmacological optimization processes. Despite the application of available tools and assays, the documentation of bona fide NecroFerrins or RIPROStatins remains particularly challenging and will likely benefit from continued interest and methodological advances in the field. Their successful clinical translation will depend on improved mechanistic understanding and the development of robust biomarkers. This emerging class of compounds may ultimately help shape future therapeutic strategies for complex human diseases that remain beyond current clinical reach.

Declarations

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Authors contribution

Delehouzé C: Conceptualization, writing-original draft, writing-review & editing.

Bach S: Supervision, Conceptualization, writing-original draft, writing-review & editing.

Conflicts of interest

Claire Delehouzé and Stéphane Bach are inventors on patents and patent applications involving ferroptosis and necroptosis. They are also founders and members of the scientific advisory board of SeaBeLife Biotech, which is developing novel therapies for treating acute and chronic organ injuries. No other conflicts of interest to declare.

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Consent to participate

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