

Paraoxonase-1 as a Therapeutic and Translational Target: Biochemical Functions, Disease Associations, Pharmacological Modulation and Future Perspectives

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Abstract

Paraoxonase 1 (PON1) is a calcium-dependent hydrolase synthesized predominantly in the liver and transported in plasma in close association with high-density lipoprotein (HDL). Although originally characterized by its capacity to hydrolyze the organophosphate metabolite paraoxon, PON1 is now recognized as a multifunctional enzyme with lactonase, arylesterase and organophosphate-hydrolyzing activities. Its biological relevance extends to the control of oxidized lipids, homocysteine thiolactone and inflammatory processes, thereby linking PON1 status with cardiometabolic, neurodegenerative and toxicological phenotypes. The marked interindividual variability in PON1 activity reflects both genetic determinants, including the Q192R and L55M variants and promoter polymorphisms, and non-genetic influences such as metabolic state, inflammation, diet and environmental exposures. This review critically summarizes the structure and catalytic biology of PON1, evaluates evidence connecting altered PON1 activity with cardiovascular disease, diabetes and metabolic dysfunction, neurodegenerative disorders, cancer and organophosphate toxicity, and discusses strategies intended to enhance or exploit PON1 therapeutically. Particular attention is given to recombinant PON1 and engineered catalytic bioscavengers, pharmacological and nutritional modulation, biomarker applications and precision-medicine approaches. Current evidence supports PON1 as a biologically informative marker and a promising translational platform; however, its clinical use remains constrained by assay heterogeneity, substrate-dependent genotype effects, incomplete mechanistic definition and limited interventional evidence. Future progress will require standardized phenotyping, carefully engineered PON1 variants, pharmacokinetic optimization and prospective studies that distinguish association from therapeutic causality.

Keywords: paraoxonase 1; PON1; HDL; oxidative stress; organophosphate toxicity; cardiovascular disease; pharmacogenetics; recombinant enzyme; precision medicine

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1. Introduction

Paraoxonase 1 (PON1) was named for its ability to hydrolyze paraoxon, the toxic oxon metabolite of the organophosphate insecticide parathion. Subsequent research substantially broadened this view. PON1 is now understood as an HDL-associated, calcium-dependent hydrolase with catalytic promiscuity toward several classes of substrates, including aromatic esters, lactones and selected organophosphorus compounds [1–3]. The enzyme is synthesized mainly in the liver, secreted into the circulation and retained on HDL through hydrophobic interactions involving its N-terminal region. This lipoprotein environment is important for PON1 stability and biological function. Interest in PON1 has increasingly shifted from its historical toxicological role toward its contribution to redox and inflammatory homeostasis. Experimental and clinical observations associate reduced PON1 activity with increased oxidized lipids, metabolic dysfunction and vascular disease, while mechanistic studies indicate that PON1 participates in the handling of lipid oxidation products and homocysteine thiolactone [2,4,5]. These functions provide a plausible biological bridge between PON1 and disorders

characterized by chronic oxidative stress and inflammation.

Nevertheless, PON1 should not be interpreted as a uniformly protective enzyme or as an established drug target across all disease states. Its measured activity depends strongly on the assay substrate, genetic background and physiological context. Associations between individual PON1 polymorphisms and clinical outcomes have also been inconsistent across populations and study designs [6–8]. A translational assessment must therefore integrate genotype, enzyme activity, HDL context and disease phenotype rather than relying on genotype alone. This review examines that integrated evidence and highlights the opportunities and limitations of PON1-directed therapeutic development.

2. Biochemistry, Structure and Genetics of PON1

2.1 Molecular structure and catalytic activities

PON1 is an approximately 43-kDa glycoprotein of 354 amino acids. Structural studies describe a six-bladed β -propeller architecture with a central tunnel containing two calcium ions. One calcium ion has a predominantly structural role, whereas the second participates directly in catalysis and substrate positioning [1–3]. The active-site environment and adjacent helices also contribute to substrate recognition and interaction with HDL.

PON1 exhibits several experimentally measurable activities. Paraoxonase activity describes hydrolysis of paraoxon and related organophosphates; arylesterase activity is commonly assessed using phenyl acetate; and lactonase activity encompasses a variety of lactone substrates. Current biochemical understanding favors lactonase activity as being closer to the ancestral or physiological function of the paraoxonase family, whereas efficient hydrolysis of particular synthetic organophosphates is substrate- and variant-dependent [2,3]. PON1 can also hydrolyze homocysteine thiolactone, a reactive metabolite capable of modifying proteins through N-homocysteinylation [2].

The relationship between PON1 and lipid oxidation is biologically important but mechanistically complex. PON1 is associated with HDL fractions that possess antioxidant and anti-inflammatory properties, and low PON1 activity is frequently accompanied by increased oxidized lipid burden [4,5]. The enzyme's function therefore needs to be considered within the broader HDL proteome and lipid environment rather than as an isolated antioxidant system.

2.2 Genetic variability and functional phenotype

The PON1 locus is highly polymorphic. Two coding variants have received particular attention: Q192R (rs662) and L55M (rs854560). Q192R alters catalytic efficiency in a substrate-dependent manner; the R192 isoform hydrolyzes paraoxon more rapidly than Q192, but the relative performance of the two isoforms differs for other substrates. L55M has been associated with differences in PON1 concentration and stability. Promoter variants, including the -108C>T polymorphism, can influence transcription and contribute to interindividual differences in circulating enzyme levels [1,2].

A critical concept is that PON1 'status' is more informative than genotype alone. Status incorporates functional enzyme activity, and ideally enzyme concentration, together with relevant genotype. This is important because environmental and metabolic factors can modify activity independently of genotype. Large genetic association studies and meta-analyses have produced heterogeneous estimates for cardiovascular outcomes, emphasizing that a single PON1 variant is unlikely to serve as a universal disease predictor [6–8].

Feature	Representative determinant	Functional relevance	Translational implication
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Catalytic structure	Two Ca^{2+} ions in β -propeller core	Structural stability and catalysis	Important for enzyme engineering
Q192R (rs662)	Q→R substitution at residue 192	Strong substrate-dependent effect on hydrolysis	Genotype must be interpreted with activity assay
L55M (rs854560)	L→M substitution at residue 55	Associated with differences in PON1 level/stability	May contribute to interindividual variability
Promoter variation	e.g., -108C>T	Influences transcription	Potential component of PON1 status
HDL association	Hydrophobic N-terminal region	Supports stability and lipid-related function	Formulation/delivery may need to mimic native environment

3. PON1 in Health and Disease

3.1 Cardiovascular disease and atherosclerosis

Among the proposed clinical roles of PON1, the cardiovascular field has the strongest historical evidence base. Oxidative modification of lipoproteins and vascular inflammation contribute to atherogenesis. PON1 resides predominantly on HDL and is linked to the ability of HDL to limit harmful lipid oxidation products. Lower circulating PON1 activity is commonly observed in dyslipidemia, diabetes and inflammatory states, and has been associated with incident or prevalent atherosclerotic cardiovascular disease [5].

Genetic evidence is less straightforward. Meta-analyses have reported small or population-dependent associations between Q192R or L55M and coronary outcomes, while large-study sensitivity analyses often attenuate these effects [6–8]. These findings argue against using a single PON1 genotype as a stand-alone cardiovascular risk marker. Functional activity, metabolic context and conventional risk factors remain essential for interpretation.

3.2 Diabetes and metabolic dysfunction

Chronic hyperglycemia, dyslipidemia and low-grade inflammation create a pro-oxidant environment that can adversely affect HDL composition and PON1 activity. Reviews of metabolic disease describe reduced PON1 activity in both type 1 and type 2 diabetes and propose bidirectional relationships among PON1, glucose homeostasis, lipid metabolism and inflammatory

signaling [9]. Glycation and oxidative modification of HDL-associated proteins may further impair PON1 function.

These observations make PON1 attractive as a marker of cardiometabolic stress, but they do not establish that raising PON1 alone will correct diabetes or its complications. Translational studies should therefore test whether PON1 modulation produces clinically meaningful effects beyond improvements in general oxidative or lipid status.

3.3 Neurodegenerative disorders

Oxidative stress and altered lipid handling are prominent features of several neurodegenerative disorders. Reduced serum PON1 activity has been reported in observational studies of Alzheimer's and Parkinson's diseases, and PON1 biology has been discussed in relation to systemic oxidative burden, pesticide exposure and vascular contributions to neurodegeneration [4]. However, circulating PON1 is not currently an established diagnostic test for these diseases.

Mechanistic interpretation also requires caution because serum PON1 does not directly equate to enzyme activity within the central nervous system. Future studies should distinguish systemic exposure biology from disease-specific neuronal mechanisms and should control carefully for age, medications, nutrition, liver function and cardiometabolic comorbidity.

3.4 Cancer

Altered PON1 concentration or activity has been described in several malignancies, consistent with the extensive remodeling of redox metabolism, inflammation and lipid handling that accompanies cancer. The direction and biological meaning of these changes can vary with tumor type and disease stage. PON1 may reflect host oxidative status rather than function as a direct tumor suppressor or oncogenic driver.

Accordingly, the concept of PON1 as an anticancer therapeutic target remains exploratory. Before therapeutic manipulation is justified, studies must clarify whether PON1 changes are causal, compensatory or simply biomarker phenomena. The broader literature on PON1-dependent anti-oxidative and anti-inflammatory pathways supports biological plausibility but also highlights incomplete mechanistic definition [4].

3.5 Organophosphate toxicity

The toxicological role of PON1 is more directly connected to catalytic function. PON1 can hydrolyze selected organophosphate oxons, but protection depends on catalytic efficiency toward the specific compound. Experiments in PON1-deficient mice demonstrated that endogenous PON1 protects against some organophosphate exposures, whereas native human PON1 is insufficiently efficient against others [10]. Thus, the presence of PON1 alone does not guarantee clinically meaningful detoxification.

This limitation has stimulated protein engineering aimed at creating recombinant PON1 variants with enhanced catalytic efficiency. Engineered recombinant human PON1 has protected experimental animals against diazoxon exposure, supporting the concept of PON1 as a catalytic bioscavenger [10,11]. More recent work continues to examine engineered variants and strategies to improve activity, stability and immunological compatibility for prophylaxis against highly toxic organophosphorus agents [12].

4. Therapeutic Strategies Targeting PON1

4.1 Pharmacological modulation

Several drug classes have been reported to modify PON1 activity or expression indirectly, particularly through changes in lipoprotein metabolism, nuclear receptor signaling or oxidative stress. Statins, fibrates and renin-angiotensin system modulators have all been investigated in this context. However, the magnitude and reproducibility of PON1 changes vary between studies, and these agents have major pharmacological actions unrelated to PON1. They should therefore not be regarded as selective PON1 activators.

A more rigorous therapeutic strategy would identify compounds that reproducibly increase PON1 expression, stabilize the active enzyme or enhance physiologically relevant catalytic functions without disrupting HDL biology. Such development requires validated screening assays using appropriate substrates and confirmation in disease-relevant models.

4.2 Diet and nutraceutical approaches

Dietary patterns rich in unsaturated fats and polyphenol-containing foods have been associated with favorable HDL function and, in some studies, higher PON1 activity. Candidate modulators include polyphenols, antioxidant vitamins and omega-3 fatty acids. These findings are biologically plausible because oxidative and inflammatory environments can suppress or destabilize PON1.

Nevertheless, dietary studies are vulnerable to confounding, and increases in measured PON1 activity should not automatically be interpreted as evidence of disease modification. Nutritional interventions are best viewed as modulators of the broader cardiometabolic environment in which PON1 operates.

4.3 Recombinant PON1 and protein engineering

Recombinant PON1 is one of the most concrete therapeutic applications of the enzyme. Development has historically been complicated by expression, folding, catalytic efficiency and stability. Engineering and optimized bacterial expression systems have enabled production of active recombinant human PON1, including variants with improved activity toward selected organophosphate substrates [10,11,13]. Key development objectives include increasing catalytic efficiency against the intended toxicant, maintaining adequate circulating half-life, minimizing immunogenicity and establishing scalable manufacturing. Fusion proteins and other engineered bioscavenger formats have also been explored [14]. For acute toxicology indications, these performance characteristics may be more important than reproducing every physiological function of native HDL-associated PON1.

4.4 Gene- and delivery-based approaches

Gene delivery, genome editing and nanotechnology are conceptually attractive because they could provide sustained expression or targeted delivery. However, these approaches remain substantially less mature than recombinant-protein strategies for PON1. Claims regarding AAV, lentiviral or CRISPR-based PON1 therapy should therefore be framed as future possibilities rather than established therapeutic platforms.

Nanocarriers may ultimately help stabilize PON1, alter pharmacokinetics or deliver PON1-modulating compounds, but formulation must preserve calcium-dependent catalytic conformation and avoid loss of activity at material interfaces. Demonstration of pharmacodynamic benefit in vivo will be necessary before targeted nanotherapy can be considered clinically credible. The major biochemical functions, disease associations, regulatory factors, and emerging therapeutic strategies related to PON1 are shown in Figure 1.

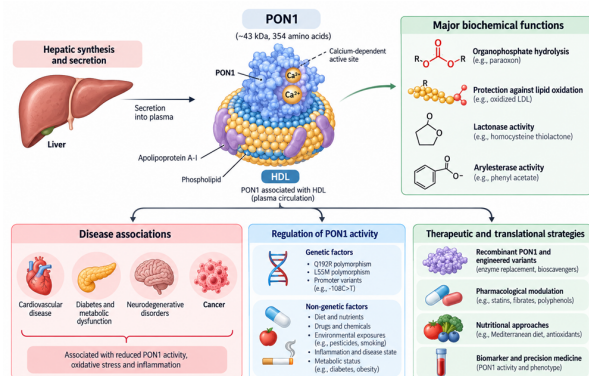


Figure 1. PON1 structure, HDL association, biochemical functions, disease associations, regulatory factors, and therapeutic and translational strategies.

5. Diagnostic, Biomarker and Precision-Medicine Potential

PON1 can be phenotyped using paraoxonase, arylesterase and other substrate-based activity assays. Because Q192R influences substrate-specific catalytic rates, assay selection is critical. A useful precision-medicine framework would combine genotype with functional activity rather than infer enzyme performance from genotype alone [1,2].

Potential applications include characterization of susceptibility to selected organophosphate exposures, assessment of dysfunctional HDL biology and research stratification in cardiometabolic disease. At present, however, assay heterogeneity and the absence of widely accepted clinical decision thresholds limit routine diagnostic use. Standardized pre-analytical conditions, reference materials and outcome-linked cutoffs are needed before PON1 testing can move from research laboratories into general clinical practice.

6. Challenges and Limitations

Challenge	Why it matters
Assay standardization	Different substrates interrogate different catalytic properties; results cannot always be compared directly.
Genotype–phenotype complexity	Q192R, L55M and promoter variants explain only part of interindividual PON1 variability.
Causality	Reduced PON1 may be a consequence or marker of disease-associated oxidative stress rather than a primary driver.
Therapeutic selectivity	Most reported pharmacological or dietary modulators act through multiple pathways and are not PON1-specific.
Protein development	Recombinant PON1 requires optimization of expression, folding, catalytic efficiency, stability and immunogenicity.
Clinical evidence	Prospective interventional trials demonstrating patient benefit from deliberate PON1 modulation remain limited.

These limitations are particularly important when translating associative biomarker findings into therapeutic claims. Future studies should report both genotype and activity where possible, specify the assay substrate and conditions, control for major metabolic and inflammatory confounders, and use prospective designs capable of testing causality.

7. Future Perspectives

- Define clinically meaningful PON1 phenotypes using standardized multi-substrate activity panels and, where feasible, direct protein quantification.
- Develop high-throughput screening platforms for selective stabilizers or modulators while confirming activity with physiologically relevant substrates.
- Engineer recombinant PON1 variants for specific toxicological targets and optimize half-life, formulation, manufacturability and immunological compatibility.
- Integrate genomics, proteomics, lipidomics and exposure data to determine when PON1 is a causal mediator, a modifier or simply a biomarker.
- Use prospective and genotype-aware clinical studies to establish whether PON1 improves risk prediction beyond established clinical variables.
- Explore targeted delivery and gene-based approaches only with rigorous pharmacodynamic validation and long-term safety assessment.

8. Conclusion

PON1 has evolved conceptually from an organophosphate-hydrolyzing enzyme into a multifunctional component of HDL biology with relevance to oxidative stress, inflammation, lipid metabolism and toxicant detoxification. The strongest translational opportunities currently lie in functional phenotyping and in engineered recombinant PON1 for selected organophosphate exposures. Associations with cardiovascular, metabolic, neurodegenerative and malignant disease are biologically compelling but require cautious interpretation because PON1 activity is influenced by genotype, substrate, environment and disease state. Consequently, future PON1 research should move beyond isolated polymorphism studies toward integrated enzyme-status measurements and mechanistically designed interventions. Such an approach will determine whether PON1 can progress from an informative biomarker and experimental bioscavenger to a validated therapeutic target in precision medicine.

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