

Taming neutrophil extravasation: a promising therapeutic approach to dampen inflammation?

Salma A. Rizo-Téllez and János G. Filep

Department of Pathology and Cell Biology, University of Montreal and Research Center, Maisonneuve-Rosemont Hospital, Montreal, Canada

Correspondence: J.G. Filep
janos.g.filep@umontreal.ca

Received: August 26, 2025.
Accepted: September 23, 2025.
Early view: October 2, 2025.

<https://doi.org/10.3324/haematol.2025.288835>

©2026 Ferrata Storti Foundation

Published under a CC BY-NC license



In the current issue of *Haematologica*, Napoli *et al.*¹ report that the dual non-competitive CXC-motif chemokine receptor 1 (CXCR1) and CXCR2 antagonist ladarixin effectively blocks transit of neutrophil granulocytes through the vascular basement membrane and extracellular matrix degradation without affecting chemotaxis and intravascular adhesion, thereby attenuating neutrophil trafficking into inflamed tissue.

Neutrophils, the most abundant immune cells in human blood, play a pivotal role in host defense against invading pathogens, but are also capable of inflicting tissue damage, a common feature of diverse inflammatory pathologies. Accumulating data challenge the simplistic view of the dichotomy of their function and indicate a role for neutrophils in orchestrating inflammation resolution and tissue repair.² In addition to functional versatility, neutrophils also exhibit phenotypic heterogeneity (neutrophil subpopulations or polarization states) under homeostasis as well as in inflammation. Correlating phenotypes with defense, injury, or repair functions is rather challenging. Universal “one size fit all” targeting approaches aimed at reducing neutrophil numbers carry the risk of impairing the defense and repair functions of neutrophils. Thus, developing more selective strategies that counter the deleterious actions (or subpopulations) of neutrophils while preserving protective functions would be highly desirable to address a yet unmet clinical need. One of the promising potential therapeutic avenues, actively pursued by several groups, including that of Napoli and colleagues,¹ is to prevent excessive tissue accumulation of neutrophils.

Neutrophil trafficking into inflamed tissues is modeled as a tightly orchestrated multistep process that has been detailed in excellent reviews.³ Among key receptors in the adhesion cascade are CXCR1 and CXCR2 expressed on neutrophils. CXCR1 and CXCR2 bind CXCL8 (in humans) and CXCL1 (in mice), which play pivotal roles in regulating neutrophil arrest on the activated endothelium and directional movement toward the inflammatory locus.⁴ Consistently, deletion of the CXCR2 gene or the dual CXCR1 and CXCR2

non-competitive allosteric inhibitor ladarixin were reported to attenuate the inflammatory response and reduce neutrophil tissue damage and disease progression in various preclinical models, including ischemia-reperfusion, type 1 diabetes and airway inflammation.⁵ Aligning with CXCL1 and CXCL8-triggered neutrophil penetration of vascular basement membrane, Napoli *et al.* identify a novel mechanism, inhibition of CXCR1/CXCR2-induced mobilization of neutrophil elastase to the cell surface and release during migration, by which ladarixin can impair neutrophil trafficking into inflamed tissue. Importantly, ladarixin showed similar efficiencies in both murine and human primary neutrophils, underscoring the translational potential of the observations. Neutrophil degradation of laminin is a prerequisite for penetrating the vascular basement membrane. Hence, the findings with ladarixin lend further support to the notion that reducing neutrophil basement membrane penetration and laminin degradation is sufficient to attenuate neutrophil extravasation without interfering with the transition from neutrophil rolling to firm adhesion to endothelial cells⁶ or internalization of CXCR2.

An unexpected finding was that ladarixin did not affect arrest of rolling neutrophils, which is governed by CXCR1/CXCR2.^{3,5} Since ladarixin acts as an allosteric efficacy inhibitor, stabilizing the receptor in a specific conformation likely prevents the activation of certain intracellular signaling pathways without affecting others upon activation by CXCR1 and CXCR2 agonists.⁷ Although the study relies on previous reports on signaling pathways, it is plausible that ladarixin exerts distinct inhibitory action on G α i2 and G α i3 proteins downstream of CXCR2, which mediate firm adhesion and neutrophil transmigration, respectively.⁸ Thus, ladarixin would selectively block the CXCR2-coupled G α i3-mediated signaling pathway, leading to Akt phosphorylation and subsequent mobilization and release of neutrophil elastase from the primary granules, without affecting CXCR2-dependent G α i2 signaling.

While ladarixin-induced attenuation of neutrophil recruitment

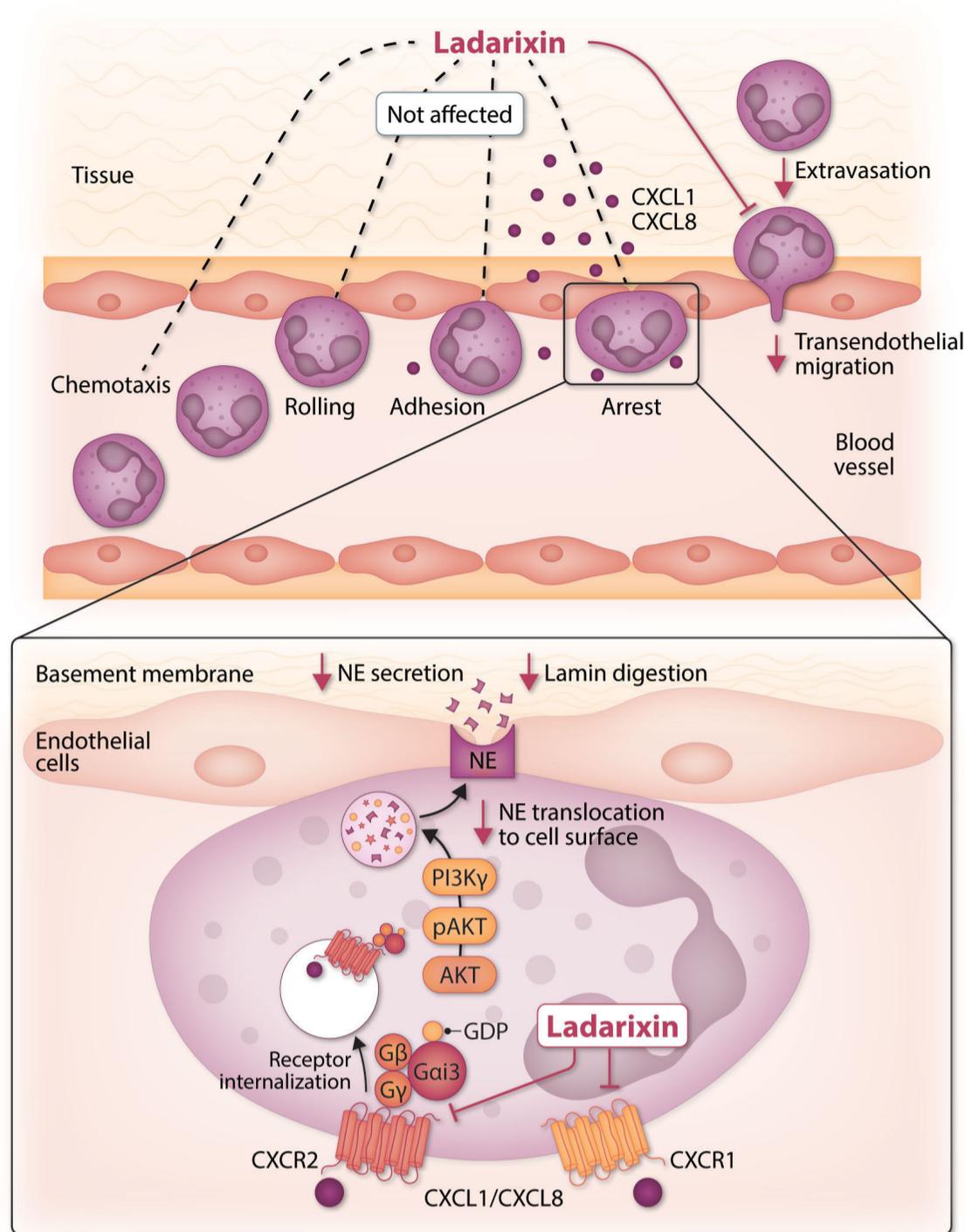


Figure 1. Proposed mechanism of action of the CXCR1/2 antagonist ladarixin for attenuating neutrophil recruitment into inflamed tissues. Ladarixin inhibits CXCR2-Gαi3 signaling to attenuate neutrophil elastase-mediated transendothelial migration without affecting neutrophil chemotaxis, rolling and adhesion to the inflamed endothelium. CXCL1: CXC ligand 1; CXCL8: CXC ligand 8; NE: neutrophil elastase; pi3Kγ: phosphoinositide 3-kinase γ; pAkt: phosphorylated Akt; Akt: protein kinase B; GDP: guanosine diphosphate; Gαi3: G protein alpha subunit 3; CXCR2: CXC-motif chemokine receptor 2; CXCR1: CXC-motif chemokine receptor 1.

is consistent with dampening the inflammatory response, surface expression of neutrophil elastase is also required for reverse endothelial transmigration of emigrated neutrophils. Inhibiting reverse transmigration may either impair clearance of emigrated neutrophils from inflamed tissues and delay timely resolution of inflammation or prevent dissemination of local inflammation and distant organ injury.⁹ Future studies should address this issue following ladarixin treatment. Of note, the proposed mechanism of action for ladarixin resembles that of nexinhib20, which selectively blocks the degranulation of azurophilic granules, including the release of neutrophil elastase.¹⁰ Local delivery of neutrophil elastase-degradable nanoparticles loaded with nexinhib20 to the airways and into emigrated neutrophils was reported to effectively reduce unrelenting neutrophil influx and de-

granulation. These observations would raise the intriguing possibility of administering ladarixin locally to achieve selective targeting of affected organs. An obvious challenge with anti-neutrophil therapies is safety, in particular predisposition to bacterial infections during long-term treatment. Although ladarixin did not affect neutrophil adhesion to the activated endothelium and only partially reduced neutrophil extravasation, it is uncertain whether this would still allow efficient neutrophil-mediated host defenses. One should also consider the potential impact of the timing of treatment with ladarixin to avoid possible interference with the repair functions of neutrophils. Translating the findings to the clinical setting will require analysis of the safety and timing of neutrophil targeting in a prospective setting.

In the recent era of recognizing the functional versatility and phenotypic heterogeneity of neutrophils, developing refined strategies to target the potentially deleterious actions (and/or subsets) of neutrophils, while preserving their function in host defense will be an important step forward to achieve this goal. While the study of Napoli *et al.*¹ raises several additional questions about molecular mechanisms and therapeutic implications, clinical trials with ladarixin should define its therapeutic potential in neutrophil-driven pathologies.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors reviewed the literature, wrote the manuscript, and designed the figure.

Funding

This work was supported by a research grant (PJT169075) from the Canadian Institutes of Health (to JGF).

References

1. Napoli M, Sitaru S, Budke A, et al. The dual non-competitive CXCR1/2 inhibitor ladarixin impairs neutrophil extravasation without affecting intravascular neutrophil adhesion. *Haematologica*. 2026;111(4):1344-1354.
2. Rizo-Téllez SA, Filep JG. Beyond host defense and tissue injury: the emerging role of neutrophils in tissue repair. *Am J Physiol Cell Physiol*. 2024; 326(3):C661-C683.
3. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol*. 2007;7(9):678-689.
4. Rot A, von Andrian UH. Chemokines in innate and adaptive host defense: basic chemokines grammar for immune cells. *Annu Rev Immunol*. 2004;22:891-928.
5. Margraf A, Ley K, Zarbock A. Neutrophil recruitment: from model systems to tissue-specific patterns. *Trends Immunol*. 2019;40(7):613-634.
6. Kurz AR, Pruenster M, Rohwedder I, et al. MST1-dependent vesicle trafficking regulates neutrophil transmigration through the vascular basement membrane. *J Clin Invest*. 2016;126(11):4125-4139.
7. Allegretti M, Bertini R, Bizzarri C, Beccari A, Mantovani A, Locati M. Allosteric inhibitors of chemoattractant receptors: opportunities and pitfalls. *Trends Pharmacol Sci*. 2008;29(6):280-286.
8. Kuwano Y, Adler M, Zhang H, Groisman A, Ley K. $G\alpha 2$ and $G\alpha 3$ differentially regulate arrest from flow and chemotaxis in mouse neutrophils. *J Immunol*. 2016; 96(9):3828-3833.
9. Nourshargh S, Renshaw SA, Imhof BA. Reverse migration of neutrophils: where, when, how, and why? *Trends Immunol*. 2016;37(5):273-286.
10. Mejias JC, Forrest OA, Margaroli C, et al. Neutrophil-targeted, protease-activated pulmonary drug delivery blocks airway and systemic inflammation. *JCI Insight*. 2019;4(23):e131468.