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Review Article

AI-Enabled Identification of Histaminergic Mechanisms Underlying Infusion-Related Dermatologic Reactions to a Targeted Oncolytic Peptide.

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Abstract

Aim: Infusion-related dermatologic reactions (IRDR) are common in oncology therapeutics, particularly among membrane-active agents, yet their underlying molecular mechanisms are often poorly defined. This lack of mechanistic clarity limits the ability to implement rational mitigation strategies and optimize clinical development. The objective herein was to determine whether artificial intelligence (AI)-based drug-target interaction (DTI) modeling can identify clinically relevant off-target mechanisms underlying IRDR observed during development of a targeted cytolytic peptide.

Design: Systems pharmacology analysis using the Operon™ AI platform, integrating multiomic, structural, pharmacokinetic, and signaling network data to predict drug-target interactions and pathway-level effects. Predictions were interpreted in the context of clinical observations from a Phase 2 oncology study.

Setting and Participants: Patients enrolled in a Phase 2 clinical trial evaluating ucalolictide (AT-101), a receptor-targeted lytic peptide, in combination with paclitaxel.

Main Outcomes and Measures: Identification of AI-predicted off-target interactions associated with IRDR and assessment of their mechanistic plausibility based on established immunologic and vascular physiology.

Results: An increased incidence of dermatologic infusion reactions was observed in patients receiving ucalolictide in combination with paclitaxel compared with paclitaxel alone. AI-based modeling identified predicted interactions between ucalolictide and histamine H1 and H2 receptors, as well as cyclooxygenase-1, implicating pathways known to regulate vasodilation, vascular permeability, and neurogenic inflammation. Although these interactions were not predicted to be high-affinity, their convergence with membrane disruption-induced immune activation and paclitaxel-associated inflammatory priming provides a mechanistically coherent explanation for the observed clinical phenotype. The rapid resolution of symptoms with antihistamines and corticosteroids further supports histamine-mediated signaling as a key contributor.

Conclusions and Relevance: AI-enabled DTI modeling identified histamine receptor-associated pathways as plausible drivers of IRDR in a membrane-active peptide therapy, demonstrating how distributed, low- to moderate-affinity interactions can become clinically significant within amplified inflammatory systems. This case study highlights the utility of AI-based systems pharmacology in elucidating mechanisms of adverse events that are not readily apparent from clinical data alone and supports its application to inform risk mitigation and guide therapeutic development.

Introduction

Infusion-related reactions remain a common and clinically significant challenge across oncology therapeutics [1]. This challenge is particularly pronounced for biologics and membrane-active agents, in which acute inflammatory responses can limit tolerability, complicate dosing strategies, and restrict patient eligibility [2]. Among these, infusion-related dermatologic reactions (IRDR), characterized by erythema, flushing, pruritus, and urticarial or morbilliform rashes, represent a frequent yet mechanistically heterogeneous toxicity phenotype arising from acute perturbations of the cutaneous neurovascular-immune unit3. Despite their prevalence, the molecular drivers of IRDR are often incompletely understood, as these reactions typically arise from the convergence of multiple overlapping pathways, including mast cell activation, complement engagement, endothelial barrier disruption, and neuroimmune signaling [3,4]. This complexity is further compounded in oncology combination regimens, where co-administered agents may synergistically amplify inflammatory signaling [5]. As a result, traditional clinical pharmacology approaches, which rely primarily on phenotypic observation and single-target attribution, are often insufficient to resolve the mechanistic basis of these events or to guide rational mitigation strategies [6]. Unlike conventional cytotoxic agents that act through intracellular targets or cell-cycle-dependent mechanisms, membrane-active oncologic therapeutics, e.g., cytolytic peptides, induce rapid biophysical perturbation of lipid bilayers, resulting in disruption of ionic gradients, osmotic destabilization, and acute cell death [7]. These agents induce biophysical membrane disruption, generating strong danger signaling and immune activation [8]. Thus, the same membrane-injury program that is therapeutically desirable (tumor killing with immune activation) can plausibly increase susceptibility to infusion-related inflammatory phenomena, especially when additional proinflammatory agents are co-administered [9]. While this property may be therapeutically advantageous by enhancing antitumor immune responses, it also introduces the potential for unintended systemic inflammatory effects, including infusion-related reactions. Importantly, these effects are unlikely to be driven by a single dominant molecular interaction but rather by distributed, low- to moderate-affinity interactions across multiple signaling networks that are highly sensitive to amplification.

Conventional approaches to identifying off-target effects, e.g., receptor binding panels or post hoc adverse event correlation, are not well suited to capturing these complex, systems-level interactions [10]. Low-affinity or context-dependent receptor interactions may not be detected in isolation but can become biologically meaningful in vivo when combined with endogenous ligand release and inflammatory priming [11]. Histamine signaling provides a paradigmatic example: even modest modulation of histamine receptor activity can produce pronounced physiological effects in tissues such as skin, where receptor density, vascular responsiveness, and neuroimmune coupling create a high gain signaling environment [12]. Accordingly, there is a critical need for integrative approaches capable of interrogating distributed pharmacologic interactions within biologically relevant network contexts.

Artificial intelligence (AI)-based drug-target interaction (DTI) modeling has emerged as a promising strategy to address this gap. By integrating multiomic data, structural features, pharmacokinetic properties, and signaling network information, AI-driven platforms can generate probabilistic predictions of both intended and off-target interactions across a broad target space [12]. Unlike traditional reductionist approaches, these models are designed to capture polypharmacology and to identify interaction patterns that may only become clinically apparent in complex physiological environments. Importantly, such approaches have the potential not only to retrospectively explain observed adverse events but also to prospectively inform mitigation strategies during drug development. In this context, we examined a clinical safety signal observed during the development of ucalolictide (AT-101), a receptor-targeted cytolytic peptide evaluated in combination with paclitaxel for the treatment of solid tumors. Ucalolictide consists of a luteinizing hormone-releasing hormone (LHRH) receptor-targeting ligand linked to a cationic membrane-disrupting peptide, enabling selective binding to LHRH receptor-expressing tumor cells followed by localized membrane lysis and immunogenic cell death. This mechanism, while therapeutically advantageous, provides a biologically plausible substrate for inflammatory activation through DAMP release and innate immune engagement [13]. During Phase 2 clinical evaluation, an increased incidence of infusion-related dermatologic reactions was observed in patients receiving ucalolictide in combination with paclitaxel compared with paclitaxel alone [14]. The clinical phenotype, characterized by flushing and rash responsive to antihistamines and corticosteroids, suggested involvement of histamine-mediated pathways; however, the molecular basis of this effect was not readily explained by known pharmacology [15].

To investigate this discrepancy, the Operon™ AI platform (GATC Health) was applied to model the drug-target interaction landscape of ucalolictide within a systems pharmacology framework. This analysis identified previously uncharacterized interactions with histamine H1 and H2 receptors, as well as cyclooxygenase-1, providing a mechanistic hypothesis linking membrane disruption-induced immune activation with amplification of histaminergic and prostanoid signaling. Notably, these interactions were not predicted to be high affinity in isolation but were consistent with a model in which non-dominant receptor engagement, when combined with endogenous mediator release and inflammatory priming (including co-administration with paclitaxel), is sufficient to produce clinically observable IRDR. This case illustrates a broader principle in translational pharmacology, i.e., adverse events in complex therapeutic systems may arise from the interaction of distributed, individually modest signals that converge within high-sensitivity physiological networks [16]. AI-based DTI modeling offers a means

to identify these interactions, contextualize them within known biology, and translate them into actionable clinical strategies. Here, we integrate clinical observations, AI-derived interaction predictions, and established immunophysiologic mechanisms to define a coherent model for histamine receptor-mediated IRDR associated with a targeted cytolytic peptide. More broadly, this work demonstrates how computational systems pharmacology can enhance mechanistic understanding of adverse events and support more precise, mechanism-informed approaches to drug development and patient management.

Despite well-characterized clinical phenotypes and an established physiological framework linking membrane disruption to inflammatory mediator release, the specific molecular drivers of infusion-related dermatologic reactions in membrane-active therapies remain incompletely defined [17]. This gap reflects a fundamental limitation of conventional pharmacologic approaches, which are typically optimized to identify high-affinity, single-target interactions but are poorly suited to resolve distributed, low- to moderate-affinity interactions that may only become biologically significant within complex, amplified inflammatory networks. Pathways such as histamine signaling and prostaglandin synthesis operate within high-sensitivity neurovascular systems in which modest perturbations can produce disproportionate clinical effects, especially in the presence of concurrent immune activation and combination therapy-induced priming. As a result, traditional adverse event attribution often fails to identify mechanistic convergence across multiple signaling axes. AI-based drug-target interaction modeling provides a systems-level approach to address this challenge by integrating structural, multiomic, and pharmacologic data to predict polypharmacologic interaction patterns and contextualize them within biologically relevant networks. Such approaches enable identification of mechanistic hypotheses that are not readily apparent through conventional methods and offer a framework for linking observed clinical toxicities to specific, testable molecular pathways.

3. Clinical Observation

During Phase 2 evaluation of ucalolictide (AT-101) in combination with paclitaxel, dermatologic infusion-related reactions were observed in 35% (8/23) of patients receiving combination therapy compared with 19% (4/21) treated with paclitaxel alone. The phenotype was characterized by erythematous flushing and rash occurring both at the infusion site and systemically, consistent with acute neurovascular cutaneous activation rather than delayed hypersensitivity. The temporal association with infusion, absence of progression to anaphylaxis, and rapid resolution following administration of diphenhydramine and corticosteroids are consistent with histamine-mediated, non-IgE-dependent pathways. Notably, prophylactic antihistamine administration prevented recurrence, indicating that the reaction was mechanistically suppressible at the level of histamine receptor signaling and downstream inflammatory amplification. The differential incidence relative to paclitaxel alone suggests that ucalolictide contributed an additive or synergistic inflammatory stimulus sufficient to cross the clinical threshold for visible rash in a primed immune environment. Contemporary analyses of infusion reactions emphasize that such events often represent convergence of multiple subclinical inflammatory inputs rather than a single high-affinity immunologic trigger, particularly in oncology combinations where endothelial activation, complement engagement, and mast cell priming coexist [18,19].

Physiological and Molecular Mechanistic Integration

The mechanistic basis for infusion-related dermatologic reactions in this context originates from the membrane-disruptive properties of cationic lytic peptides, which interact electrostatically with negatively charged phospholipids to destabilize lipid bilayers and induce rapid ionic flux and cellular injury [20]. This membrane perturbation not only mediates tumor cell lysis but also initiates innate immune activation through release of damage-associated molecular patterns such as ATP and HMGB1 and through complement activation, generating anaphylatoxins capable of stimulating mast cell degranulation [21]. The resulting release of histamine and lipid mediators, including prostaglandins, produces potent vasodilatory and permeability effects within the cutaneous microvasculature, manifesting clinically as erythema, flushing, and pruritus. These responses are amplified by the high gain signaling properties of histamine receptors, in which even limited receptor engagement can potentiate endogenous mediator effects, particularly in inflamed tissue environments [22]. Concurrently, prostaglandin production further augments vascular responses, lowering the threshold for clinically apparent reactions [23]. These properties create a mechanistic context in which infusion-related inflammatory reactions may arise, but the precise molecular drivers remain undefined. In combination regimens, this susceptibility is further heightened by agents such as paclitaxel, which promote mast cell activation and inflammatory priming, thereby amplifying downstream neurovascular responses.

5. AI-Based Target Interaction Findings

To investigate potential mechanistic drivers beyond nonspecific inflammatory activation, AI-based drug-target interaction modeling using the Operon™ platform was applied to ucalolictide. In addition to its intended interaction with luteinizing hormone-releasing hormone receptors, the analysis identified predicted off-target interactions with histamine H1 and H2 receptors, as well as cyclooxygenase-1. These targets are centrally involved in regulating vasodilation, vascular permeability, and neurogenic inflammation, providing a biologically coherent link to the observed dermatologic infusion reactions. Although these interactions are not expected to represent primary high-affinity binding events, their convergence within histaminergic and prostanoid signaling pathways suggests that even modest receptor engagement may

amplify endogenous inflammatory responses, particularly in the context of membrane disruption-induced immune activation. This system level interaction profile is consistent with a mechanism in which distributed, low-intensity pharmacologic effects become clinically significant through amplification within high-sensitivity neurovascular and immune signaling networks.

Mechanistic Model of IRDR

Consistent with these predictions, the observed clinical phenotype can be understood as the result of a convergent, feed-forward inflammatory cascade in which membrane disruption initiates innate immune activation that is subsequently amplified through histamine receptor-mediated and prostaglandin-dependent signaling pathways. The initiating event is biophysical membrane disruption, which induces rapid ionic flux and release of DAMPs such as ATP and HMGB1 [24]. These endogenous danger signals activate pattern-recognition receptors on resident immune cells and promote complement cascade engagement, generating anaphylatoxins capable of directly stimulating mast cells [22,25]. Mast cell degranulation results in immediate release of histamine and preformed mediators, followed by synthesis of lipid-derived autacoids including PGD_2 and leukotrienes, thereby creating a highly vasoactive microenvironment [26]. Within this context, even moderate direct interaction of ucalolictide with histamine H1 and H2 receptors may be sufficient to augment endogenous histamine signaling. Histamine receptors are prototypical high-amplification GPCRs characterized by receptor reserve, dynamic desensitization, and context-dependent signaling bias [27]. Contemporary pharmacologic analyses emphasize that partial agonism or low-affinity engagement can significantly modulate signaling tone when endogenous ligand concentrations are elevated, particularly in inflamed tissue where receptor expression and G-protein coupling efficiency may be enhanced [28,29]. H1 receptor activation increases intracellular Ca^{2+} and nitric oxide production in endothelial cells, driving vasodilation and increased vascular permeability, while H2 receptor-mediated cAMP signaling synergistically augments vasorelaxation and prolongs hyperemic responses [30]. The predicted interaction with cyclooxygenase-1 further potentiates this cascade by facilitating prostaglandin synthesis from arachidonic acid liberated during mast cell activation. PGD_2 and related prostanoids enhance cutaneous vasodilation and contribute to erythema and pruritus, reinforcing the visible dermatologic phenotype [31].

Paclitaxel co-administration provides an additional priming layer [32]. Taxanes are associated with complement activation, endothelial perturbation, and mast cell-dependent and independent hypersensitivity phenomena, even in the absence of IgE-mediated allergy [33]. Inflammatory priming increases endothelial responsiveness and lowers the threshold for vasodilatory mediator effects. The integration of membrane injury, DAMP signaling, mast cell degranulation, GPCR-amplified histamine signaling, prostaglandin synthesis, and taxane-associated immune activation establishes a coherent pathophysiologic sequence culminating in acute flushing and rash. These findings support a multi-pathway amplification mechanism consistent with the observed clinical phenotype.

Clinical Correlation

The rapid resolution of symptoms with diphenhydramine supports a dominant role for H1 receptor-mediated neurovascular signaling. Corticosteroid responsiveness further implicates transcriptionally regulated inflammatory mediators, including cytokines and eicosanoids, which are attenuated through glucocorticoid receptor-dependent suppression of NF-κB and AP-1 pathways [34]. The absence of hypotension, bronchospasm, or progressive systemic involvement argues against classical IgE-mediated anaphylaxis and aligns more closely with non-IgE-dependent mast cell activation syndromes such as vancomycin-associated infusion reactions [35]. Current clinical guidance for infusion reactions to biologics and taxanes supports antihistamine premedication in patients with prior reactions or high-risk regimens, reflecting established efficacy of H1 blockade in attenuating cutaneous vasodilatory manifestations [36]. The prevention of recurrence with prophylactic antihistamines in this setting is therefore mechanistically concordant with histamine-driven amplification as a key effector pathway.

Implications for Drug Development

This case underscores the translational importance of systems-level pharmacology in the development of membrane-active oncologic agents. First, it illustrates that moderate off-target interactions within high-gain GPCR networks can become clinically significant when embedded in an inflammatory context, challenging the assumption that only high-affinity binding events warrant attention during safety evaluation. Contemporary GPCR pharmacodynamics increasingly recognize the relevance of signaling bias, receptor reserve, and tissue-specific amplification in determining in vivo effects [37]. Second, it highlights the necessity of integrating immunologic and vascular physiology into safety modeling for lytic peptides, whose therapeutic mechanism intrinsically engages innate immune pathways. Third, it demonstrates the operational value of AI-based drug-target interaction modeling in identifying plausible mechanistic drivers before large-scale Phase 3 exposure amplifies adverse event signals. As oncology drug development increasingly relies on rational combination regimens, anticipatory modeling of pathway convergence becomes critical for distinguishing manageable inflammatory phenomena from structural toxicity [38].

Limitations and Future Directions

The mechanistic inferences presented here derive from computational predictions that have not yet been confirmed by orthogonal biochemical assays. Bioactivity scores generated by AI platforms represent probabilistic interaction estimates rather

than measured equilibrium dissociation constants and therefore cannot be directly equated with in vivo receptor occupancy. The clinical dataset is limited in size and was not powered for mechanistic correlative analyses. Prospective validation should include radioligand binding or functional signaling assays to quantify H1R and H2R engagement, mast cell degranulation assays to evaluate direct activation potential, measurement of circulating histamine, tryptase, and prostaglandin metabolites during infusion, and pharmacokinetic-pharmacodynamic modeling to optimize antihistamine prophylaxis strategies. Incorporation of complement activation markers and endothelial permeability biomarkers would further refine causal attribution.

Conclusion

AI-enabled drug-target interaction modeling identified histamine receptor-associated pathways and prostaglandin signaling as plausible contributors to infusion-related dermatologic reactions observed with ucalolictide in combination therapy. By linking predicted off-target interactions to the observed clinical phenotype, this approach provides a mechanistically grounded explanation that was not apparent from clinical data alone. These findings directly informed mitigation strategies, including antihistamine prophylaxis, and illustrate how AI-based systems pharmacology can enhance detection of clinically relevant polypharmacology, support mechanism-informed safety management, and de-risk therapeutic development.

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