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Targeting GSDMD-mediated pyroptosis: An AI-guided peptide discovery

Weili Wang,[1] Qiming Liang,[1,2,*] and Chunxia Wang[1,*]

[1]Institute of Pediatric Infection, Immunity, and Critical Care Medicine, Shanghai Children's Hospital, Shanghai 200062, China

[2]Shanghai Institute of Immunology, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

*Correspondence: liangqiming@shsmu.edu.cn(Q. L.); karencx0465@163.com (C. W.)

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Inflammation is a double-edged sword. It is a crucial protective response to infection or injury, but when dysregulated, it can lead to chronic diseases and tissue damage. Pyroptosis, a form of inflammatory cell death mediated by the gasdermin family of proteins, has emerged as a key player in various pathological conditions, including sepsis, cytokine release syndrome, and autoimmune disorders.[1] As a central executioner of pyroptosis, Gasdermine D (GSDMD) is cleaved by inflammatory caspases, such as caspase-1 and caspase-4/5 in human or caspase-11 in mice, releasing its N-terminal domain (GSDMD-NT), which oligomerizes and forms pores in the cell membrane.[1,2] These GSDMD-NT pores disrupt cellular integrity, leading to the release of pro-inflammatory cytokines like interleukin-1β (IL-1β) and IL-18, and ultimately, pyroptotic cell death.[3,4] Therefore, targeting GSDMD-mediated pore formation represents a promising therapeutic strategy for mitigating inflammation in a wide range of conditions.

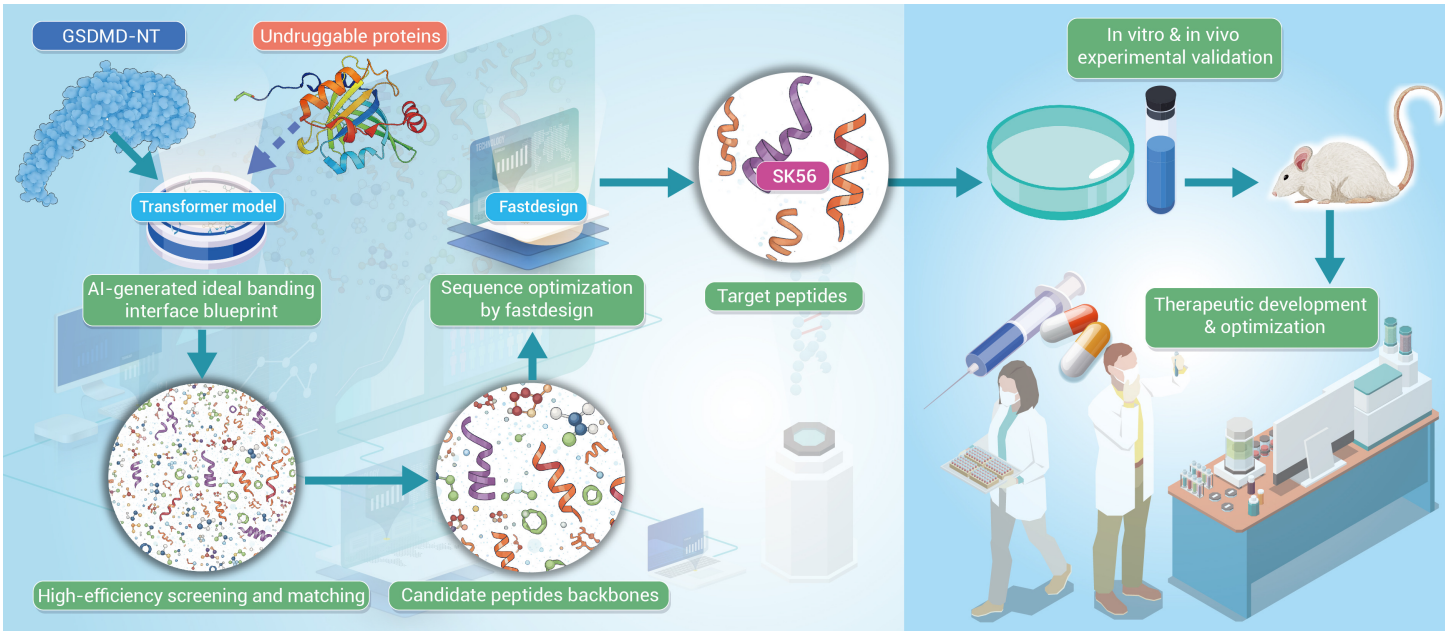

Figure 1. Schematic of AI-Driven peptide drug design and validation workflow for undruggable proteins.

In a recent study published by Sun et al. in Nature Immunology, the authors leverage artificial intelligence (AI) to screen and identify a novel peptide, SK56, which acts as a GSDMD pore blocker, effectively delaying pyroptosis and reducing the inflammatory response in various in vitro and in vivo models.[5] The authors address the challenge of identifying GSDMD pore blockers by employing an AI-driven approach. They utilize a deep learning model, Transformer, trained on a large dataset of protein structures and interaction interfaces (approximately 40,000 experimentally validated protein-protein interaction interfaces from the Protein Data Bank [PDB]). The model is adapted to process protein structures based on atomic coordinates, atom type, and charge information to generate surface interactions as output. Leveraging this computationally derived blueprint of the ideal GSDMD-NT binder, the authors moved to high-efficiency virtual screening and matching against a pre-built library of peptide backbones. This virtual screening process rapidly narrowed down the vast chemical space to a manageable set of promising candidates. To refine these candidates and optimize their sequences for enhanced binding affinity and stability, the team utilized Rosetta FastDesign software, culminating in the identification of 12 top-performing peptide candidates. Through rigorous virtual and in vitro experimental validation of these 12 candidates, the team ultimately confirmed the significant inhibitory effect of SK56 on the formation of the GSDMD-NT pore, establishing it as a promising lead compound.

Since SK56 directly and specifically interacts with GSDMD-NT, it does not interfere with the upstream events in the pyroptotic pathway, such as inflammasome activation, caspase-1 activation, GSDMD cleavage, or IL-1β processing. However, SK56 significantly reduces pyroptosis and IL-1β release in THP-1 cells and BMDMs stimulated with LPS and nigericin. Furthermore, SK56 reduces mitochondrial damage in pyroptotic cells, suggesting that it protects mitochondrial integrity by blocking GSDMD-NT pores on the mitochondrial membrane. Mechanistically, SK56 binding to GSDMD-NT pores alters the surface charge characteristics of the pore, potentially disrupting its ability to conduct ions and release cytokines. In addition, SK56's inhibition of pyroptosis appears to be dependent on the endosomal sorting complexes required for transport (ESCRT) mediated membrane repair system, as indicated by CHMP4-GFP puncta formation in treated cells, consistent with engagement of ESCRT-dependent repair following pore inhibition. In both lipopolysaccharide (LPS)- and cecal ligation and puncture (CLP)-induced delayed-treatment sepsis models, administering SK56 after disease induction to assess therapeutic efficacy significantly decreased the levels of proinflammatory cytokines, such as IL-1β, TNF-α, and interferon-γ (IFN-γ), in the peripheral blood and reduced organ damage in the lung, kidney, liver, intestine, and spleen, leading to a significant improvement in survival rates.

This multi-stage AI-driven approach offers significant advantages over traditional high-throughput screening. First, it also provides a novel solution

for targeting proteins previously considered "undruggable." The Transformer model's core capability lies in its ability to design a binding partner "from scratch" for targets that lack well-defined binding pockets. This is particularly relevant for smooth protein surfaces like GSDMD-NT, where traditional small-molecule drug design is challenging. However, its applicability extends beyond GSDMD, offering a pathway to designing highly specific peptide inhibitors for other critical protein interfaces that are currently inaccessible to small-molecule drugs. Second, this approach boasts exceptionally high screening efficiency. Through the combined power of virtual screening and generative design, the authors drastically reduced the number of candidate molecules requiring costly and time-consuming experimental validation. This not only saves immense resources in synthesis and testing but also significantly accelerates the overall drug discovery cycle. Third, this methodology represents a fundamental paradigm shift from "finding a drug" to "designing a drug." The process is no longer limited to screening existing compound libraries. Instead, it enables researchers to rationally and creatively construct novel solutions based on the intrinsic physicochemical properties of the target molecule, opening up a new frontier in drug design.

While the AI-driven approach presented by Sun et al. holds immense promise,[5] it's crucial to acknowledge the current limitations and challenges associated with this emerging paradigm. First, the performance of the Transformer model is intrinsically linked to the quality and diversity of its training data. The AI's predictive power is derived from the patterns and relationships it learns from the PDB. Consequently, if the interaction motifs of a target protein, such as GSDMD-NT, are underrepresented within the PDB, the model's accuracy may be compromised. This could potentially lead to biased screening outcomes, where the identified candidates are not truly optimal binders. Second, the current methodology remains constrained by the scope and diversity of the pre-built scaffold library. While the AI designs an ideal binding interface, the final candidate molecule must be identified through a process of matching and optimization within a finite library of peptide backbones. The limited diversity of this library inherently restricts the potential to identify a molecule that closely approximates the theoretically optimal solution. A critical future direction will be to integrate this approach with AI models capable of generating novel protein backbones de novo, thereby eliminating the reliance on pre-existing scaffolds. Third, peptides, as a therapeutic class, present their own set of inherent challenges that must be addressed. These include issues of in vivo stability (susceptibility to degradation by proteases), delivery efficiency (difficulty crossing cell membranes and reaching target tissues), and potential immunogenicity (eliciting an unwanted immune response). All of these factors necessitate careful consideration and subsequent medicinal chemistry optimization to enhance the therapeutic potential of SK56 and other peptide-based GSDMD inhibitors.

In conclusion, the work by Sun et al. is of profound significance. It not only presents a promising therapeutic candidate, SK56, for the treatment of inflammatory diseases but, perhaps more importantly, successfully implements and validates a brand-new paradigm for drug discovery. This research powerfully demonstrates that by leveraging AI to deeply understand and exploit the physicochemical properties of a target protein's surface, including shape complementarity and electrostatic potential, it becomes possible to rationally design molecules with high binding potential. This capability has the potential to bring a vast number of targets once deemed "undruggable" within reach of therapeutic development (Figure 1). Empowered by AI, the scientific community can now pursue even more ambitious goals, including the design of functional agonists to fine-tune protein activity, molecules that stabilize or disrupt specific protein conformations for long-term functional modulation, and agents that target transient protein intermediates for more sophisticated biological interventions. Indeed, the engineering of novel biologics with unprecedented function is accelerating, driven by the synergistic integration of powerful design and optimization tools. Cutting-edge examples include RFpeptides from the David Baker lab, which can de novo design highly stable and potent cyclic peptide backbones, and complementary software like ProteinMPNN that rapidly optimizes their sequences with superior precision. This powerful synergy exemplifies a fundamental shift, as AI empowers life scientists to move beyond observation and become true "engineers" of life, capable of actively and rationally modulating its core processes.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.