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Editorial

Oral administration of 4′-fluorouridine provides a breakthrough for Lassa fever therapy

Lassa fever is a fatal hemorrhagic fever caused by Lassa virus (LASV), with 300,000–500,000 infections and 5000–6000 deaths annually in West Africa, and the mortality rate can exceed 30 % in severe hospitalized patients. However, no licensed vaccines or specific therapeutics are currently available clinically for Lassa fever; ribavirin, the most commonly used drug, shows controversial efficacy and teratogenicity, other candidates such as favipiravir require intravenous administration, and monoclonal antibody therapies are limited by delivery routes and high costs. Therefore, the development of safe, potent, and easily administrable novel antiviral agents is an urgent requirement for the prevention and control of Lassa fever. Initially developed as a potent inhibitor of influenza virus and respiratory syncytial virus (RSV), 4′-fluorouridine (4′-FlU, EIDD-2749) was identified through systematic chemical modifications of nucleoside scaffolds to enhance oral bioavailability and target-specific binding to viral RNA-dependent RNA polymerase (RdRp). 4′-FlU is a broad-spectrum and orally bioavailable nucleoside analog, whose broad antiviral activity against a variety of RNA viruses has been demonstrated in preclinical studies. It exerts its antiviral effect by inhibiting the RdRp and blocking viral replication *via* the induction of immediate chain termination of viral RNA synthesis.

First, a study published in *Science Translational Medicine* by the Flint team systematically evaluated the therapeutic efficacy of 4′-FlU in a lethal guinea pig model of Lassa fever [1]. The study demonstrated that 4′-FlU not only exhibited excellent pharmacokinetic properties with wide tissue distribution and no obvious toxicity, but also showed significant efficacy in the lethal guinea pig model even at low doses and with delayed administration. Although 4′-FlU displayed prominent late-stage therapeutic effects in the guinea pig model, this model has notable limitations: it cannot accurately recapitulate the pathological features of human Lassa fever, and only supports a limited number of LASV strains, making it difficult to cover the viral genetic diversity, especially the more pathogenic variants such as the lineage VII Togo strain. In addition, *in vitro* studies revealed that 4′-FlU showed the lowest inhibitory activity against the Togo strain, further highlighting the necessity of verifying its antiviral efficacy *in vivo*.

Against this background, a landmark study published in *Nature* by the Geisbert team [2] validated the potential of the oral nucleoside analog 4′-FlU in the treatment of infections caused by LASV lineage VII (Togo strain), representing a critical step forward in antiviral drug development. Although the Geisbert group had previously established a LASV Togo strain model in cynomolgus monkeys, they found that Arevirumab-3, a monoclonal antibody, exhibited poor efficacy against this strain. Furthermore, the coronavirus disease 2019 (COVID-19) pandemic led to a shortage of cynomolgus monkeys. As an alternative, the Geisbert team adopted the African green monkey (AGM) model [3], which had been shown to better recapitulate the features of human disease when infected with the LASV lineage II Nigerian strain. On this basis, the group first established an AGM model infected with the LASV lineage VII Togo strain, and then performed therapeutic efficacy evaluation of 4′-FlU in this model.

In this study, the more pathogenic lineage VII Togo strain of LASV was used. To address the reduced efficacy of monoclonal antibodies, a clinically relevant infection scenario was simulated. Six days after infection (when the monkeys had developed viremia and clinical signs including fever and lymphopenia), five monkeys were administered 5 mg/kg 4′-FlU orally once daily for 10 consecutive days, with one monkey serving as an untreated positive control. All monkeys exhibited obvious clinical symptoms and abnormal pathological markers before treatment.

Results showed that all five treated monkeys survived to the 32-day study endpoint, among which four rapidly cleared circulating infectious virus. Fever resolved promptly after treatment, and appetite as well as clinicopathological parameters gradually returned to normal. Viral load analysis confirmed that four treated monkeys completely cleared viral RNA and infectious virus at the endpoint, while one still had a low level of virus but with a decreasing trend. The control group exhibited higher and delayed viral peak titers; the treated group showed significantly reduced tissue viral loads, with minimal infectious virus detected in immune-privileged tissues. Surviving monkeys developed moderate glycoprotein complex (GPC)-specific IgG at 12–21 days, and neutralizing antibody titers increased over time, whereas no IgG was detected in the control group.

Pathological examination revealed multiple organ lesions and extensive LASV antigen positivity in the control group. In contrast, the treated group showed no obvious gross lesions; only 2 animals exhibited mild inflammation with no evidence of LASV antigen staining. Transcriptomic analysis confirmed that 4′-FlU supports viral clearance and immune reconstitution by attenuating deleterious inflammatory responses and enhancing protective cellular immunity, thus demonstrating significant therapeutic and protective efficacy against lineage VII LASV infection. This study successfully established an AGM model of lineage VII Togo strain LASV, providing critical non-human primate experimental support for the further development of this agent and the exploration of oral antiviral therapies for Lassa fever (Fig. 1).

Geisbert's study, using the AGM model and the lineage VII Togo strain under a post-exposure treatment scenario (5 mg/kg, 6 DPI),

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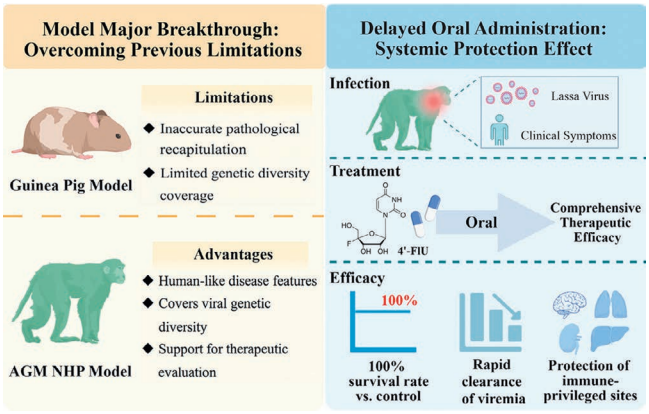


Fig. 1. Mechanism of action and antiviral efficacy of 4′-FlU against LASV. Created with BioGDP.com.

validated the efficacy, safety, and convenience of 4′-FlU as an oral agent for the treatment of Lassa fever. Its oral administration, which does not require intravenous injection, overcomes the application bottlenecks of traditional therapies in resource-limited regions. 4′-FlU can not only be used for the treatment of clinically symptomatic infected patients but also holds potential as a post-exposure prophylactic to control outbreaks. Meanwhile, its remarkable efficacy against the highly pathogenic lineage VII virus, activity at low doses, and broad-spectrum antiviral properties further enhance its public health value.

The remarkable late-stage therapeutic efficacy of 4′-FlU against Lassa fever in nonhuman primate models provides important insights for medicinal chemistry research, 4′-substituted nucleoside analogs targeting RdRp [4] show broad-spectrum anti-RNA virus potential, laying a foundation for the development of broad-spectrum antiviral agents. Furthermore, it is necessary to clarify the cryo-electron microscopy structure of the 4′-FlU and L protein complex of the LASV, and to explore its mechanism of action. This is of great significance for rational drug design and subsequent development. Nevertheless, its dosage regimen requires further optimization, long-term safety remains to be comprehensively evaluated, and clinical translation needs systematic advancement. Therefore, future studies are warranted to validate the efficacy of delayed administration at more advanced disease stages, assess the risk of viral latency and the protective effect against long-term sequelae of Lassa fever, accomplish systematic toxicological and safety evaluations, clarify the pharmacokinetic interactions between this compound and the supportive therapeutic drugs for Lassa fever, as well as expand animal sample sizes and diversify experimental animal models to verify the generalizability of the research findings.

This case of 4′-FlU for Lassa fever therapy perfectly illustrates that pharmaceutical innovation is not merely confined to the innovation of chemical structures, but more crucially, it is oriented towards unmet clinical needs. Achieving successful drug repurposing necessitates strengthened interdisciplinary collaboration [5], for instance, close cooperation between medicinal chemists, pharmacologists, clinicians and other professionals in the pharmaceutical research and development chain. To further illustrate the value of interdisciplinary drug repurposing, two representative cases are presented below. A striking domestic example in China is the research and development of Selaviroc, a novel candidate drug with independent intellectual property rights. The rapid selection of repurposed drugs relies on high-throughput screening of existing clinical-stage libraries and the utilization of established safety profiles, which can bypass early phase I toxicity trials and significantly compress the development timeline during public health emergencies. Originally developed as a C–C chemokine receptor type 5 (CCR5) antagonist for human immunodeficiency virus (HIV) treatment and approved for clinical trials in 2019, Selaviroc has been repurposed through in-depth mechanistic research which identified CCR5 as a potential novel target for both multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). Subsequent preclinical studies confirmed its superior therapeutic effects compared with positive control drugs in animal models of MS and ALS, leading to its approval for clinical trials for these two neurological diseases in 2025 and 2026 respectively. Similarly, in the realm of antiviral nucleoside, Bemnifosbuvir (BEM, AT-527) serves as another highly compelling recent example of drug repurposing. BEM is a nucleotide analogue previously characterized with potent pan-genotypic activity against hepatitis C virus (HCV) and other RNA viruses. Recently, BEM was successfully repurposed to target the hepatitis E virus (HEV), demonstrating efficient suppression of HEV replication *in vitro* and *in vivo*. Crucially, it significantly reduced HEV viral loads and liver inflammation in a preclinical gerbil infection model. These remarkable achievements are the result of cross-institutional and interdisciplinary collaboration among Chinese research teams, fully embodying the core value of synergy in drug research and development.

In summary, this study using an African green monkey model infected with the highly pathogenic lineage VII Togo strain of LASV demonstrates that oral 4′-FlU exhibits remarkable therapeutic efficacy against advanced Lassa fever, providing critical preclinical evidence for the development of broad-spectrum nucleoside antiviral agents targeting RdRp. Further investigations are warranted to expand the late therapeutic window, optimize dosage regimens, and evaluate long-term safety, thereby accelerating its clinical translation, laying a solid foundation for human clinical trials. More importantly, the repurposing of 4′-FlU and the developments of Selaviroc and Bemnifosbuvir for new indications both reveal a universal truth for pharmaceutical research and development: the successful creation of innovative drugs is a collective outcome of diligence and perseverance, flexibility and insight, as well as unity and collaboration. These essential qualities carry profound and universal enlightening significance for the global research and development of drugs targeting severe viral infectious diseases, guiding researchers to focus on clinical needs, strengthen interdisciplinary cooperation, and explore more efficient drug development strategies to address the global challenges posed by emerging and re-emerging infectious diseases.

CRediT authorship contribution statement

Qi Zheng: Writing – original draft. **Xiaoyi Hu:** Writing – review & editing. **Linan Wu:** Writing – review & editing. **Wenzhong Zhou:** Writing – review & editing, Funding acquisition. **Peng Zhan:** Writing – review & editing, Funding acquisition. **Shenghua Gao:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] S.R. Welch, J.R. Spengler, J.B. Westover, et al., Sci. Transl. Med. 16 (2024) eado7034.
[2] R.W. Cross, J. Turcinovic, A.N. Prasad, et al., Nature 650 (2026) 961–969.
[3] R.W. Cross, A.N. Prasad, J. Turcinovic, et al., Cell. Rep. Med. 6 (2025) 102263.
[4] X. Hu, S. Gao, P. Zhan, Chin. Chem. Lett. 37 (2026) 111876.
[5] S. Tuci, B. Mercorelli, A. Loregian, Pharmacol. Ther. 273 (2025) 108903.