frontiers | Frontiers in Virology

TYPE Opinion
PUBLISHED 14 November 2024
DOI 10.3389/fviro.2024.1458112

OPEN ACCESS

EDITED BY
Tsutomu Murakami,
National Institute of Infectious Diseases (NIID), Japan

REVIEWED BY
Athanasios Kossyvakis,
Ministry of Health (Greece), Greece
Yuta Hikichi,
National Cancer Institute at Frederick (NIH), United States
Eriko Padron-Regalado,
Centers for Disease Control and Prevention (CDC), United States

*CORRESPONDENCE
David E. Martin
drdavidemartin@aol.com

RECEIVED 01 July 2024
ACCEPTED 31 October 2024
PUBLISHED 14 November 2024

CITATION
Martin DE and Tripp RA (2024) Host-directed antiviral therapeutics and the NIAID research agenda: an underexplored frontier.
Front. Virol. 4:1458112.
doi: 10.3389/fviro.2024.1458112

Host-directed antiviral therapeutics and the NIAID research agenda: an underexplored frontier

David E. Martin[1]* and Ralph A. Tripp[2]

[1]TrippBio Inc, Jacksonville, FL, United States, [2]Department of Infectious Disease, University of Georgia, Athens, GA, United States

KEYWORDS

host-directed therapies, direct acting anti-viral drugs, NIAID, influenza, coronavirus (CoV), pandemic preparedness

Introduction

Recent human cases of influenza A H5Nx virus infection and mortality have raised epidemic concerns. The recent fatal case of H5N2 in Mexico, as reported by the World Health Organization (WHO) (1), and the reports of Eurasian lineage goose/Guangdong clade 2.3.4.4b H5N1 infections in cows, which sickened three people who had close contact (2), highlight the urgency of addressing H5Nx infections in humans. On June 5, 2024, the National Institutes of Allergy and Infectious Diseases (NIAID) released the NIAID Research Agenda for 2024 H5N1 Influenza (3). This agenda outlines four key objectives for understanding the biology of the H5N1 virus and advancing virus detection, treatment, and prevention strategies. Within each objective, focus areas define the active areas of research and investigation. The third objective centers on advancing existing and novel treatment strategies, including Direct-Acting Antivirals (DAAs) and monoclonal antibodies. While Host-Directed Antivirals (HDAs) are mentioned, it is unclear why HDAs were not prominently included in this objective. This is an important consideration as this Research Agenda will direct the significant investments from NIAID toward the areas of interest.

There are two approaches to developing antiviral drugs, i.e., drugs directly interacting with specific viral targets to disrupt their replication and infection, known as DAAs (4), and drugs that target human proteins and interfere with host genes and pathways rather than the virus, known as HDAs (5, 6). HDAs present several compelling advantages over traditional DAAs and should be included in the NIAID Research Agenda. One compelling reason is the reduced probability of developing viral resistance because HDAs target host cell pathways that are essential for viral replication rather than the virus. It is well-understood that viruses rapidly mutate, often rendering DAAs ineffective over time,while HDAs target host factors and offer a more durable antiviral strategy (7). A second reason is that the activity of HDAs is often broad-

spectrum because several host pathways used for virus replication are often shared, and targeting these common pathways has the potential to be effective against a range of viruses. This broad-spectrum activity is particularly valuable in treating emerging and re-emerging viral infections where the specific pathogen may not be immediately known. A third reason is by combining HDA and DAA drugs having with different mechanisms of action they can enhance antiviral efficacy. HDAs can complement the action of DAAs by disrupting the virus's ability to exploit host machinery, while DAAs directly inhibit viral replication. This synergy can lead to more effective treatment regimens and potentially lower doses of each drug, reducing toxicity and side effects. Another reason for evaluating HDAs is because they work by modulation of the host's immune response, potentially reducing the harmful effects of inflammation and promoting a more balanced immune reaction. This is particularly important in viral infections where the immune response, rather than the virus itself, causes significant damage, as seen in severe influenza and COVID-19 cases (8). Finally, the identification of host pathways involved in viral replication and the immune response has the potential to drive innovative approaches to antiviral drug discovery and the development of novel treatment options.

Despite their potential, discovering and developing HDAs is burdened with challenges which may discourage HDA prioritization in NIAID's funding and research agenda. Specifically, the identification of host targets that can be modulated without causing considerable toxicity to the host is a concern. Host pathways are often fundamental for cellular function making targeting of the pathway difficult without adverse effects. Ensuring the safety of HDAs requires extensive preclinical and clinical testing to balance efficacy and toxicity. Additionally, the interactions between viruses and host cells are complicated and poorly understood, making identifying suitable host targets challenging. Understanding these interactions requires advanced technologies such as high-throughput screening, systems biology, and sophisticated bioinformatics tools. Moreover, viruses can manipulate multiple host pathways, adding further complexity to target identification, and there can be substantial variability in host responses due to genetic, epigenetic, and environmental factors. This variability can potentially complicate the development of universally effective HDAs. Apart from the scientific challenges, there are often regulatory challenges related to repurposing existing drugs for new indications, as gaining regulatory approval for a new class of antivirals can be more complex than traditional DAAs (9) and pharmaceutical companies may hesitate to invest in HDAs, particularly those repurposed from other indications as these products may lack sufficient patent coverage for the new indications to justify the development and commercialization costs. Finally, NIAID has traditionally focused on DAAs and monoclonal antibodies where the science, while still complex, is often more straightforward with a longer record of success.

Government funding is crucial in adopting the challenges associated with HDA development and ensuring the progression of this promising therapeutic approach. Discovering viable HDA targets requires broad basic research to understand host-virus interactions. This funding can support universities, research institutions, and collaborative projects that focus on unraveling these complex biological mechanisms. This translational research bridging the gap between basic science and clinical application also requires considerable resources for validating targets and developing initial therapeutic candidates. Identifying new and novel methods for antiviral treatment reduction involves risk and uncertainty, which can reduce the appetite for private investment. Government funding can de-risk these investments by providing initial capital for early-stage research and development. Government-funded projects can attract further private-sector investment and partnerships by demonstrating proof of concept and initial safety. In addition, government funding can prioritize the development of HDAs that are accessible and affordable for all populations, particularly those that have been repurposed. This is important for ensuring equitable access to antiviral treatments in low- and middle-income countries, where commercial incentives may be limited.

To address the growing threat of H5Nx and other respiratory viruses with pandemic potential, NIAID must incorporate HDAs into its research agenda. This inclusion would diversify the available antiviral strategies and provide a more robust response to emerging viral threats. The rationale for excluding HDAs is not scientifically justified, especially given the potential benefits and the evidence supporting their use in combination with DAAs.

Specifically, NIAID should:

1. Allocate Specific Funding for HDA Research: Designate a portion of its budget for discovering and developing HDAs. This funding should support both basic and translational research efforts.
2. Foster Collaborative Research Initiatives: Encourage collaborations between academic institutions, industry, and government agencies to leverage diverse expertise and resources. These collaborations can accelerate the identification of viable HDA targets and the development of therapeutic candidates.
3. Integrate HDAs into Existing Programs: Expand the scope of current antiviral research programs, such as the Antiviral Drug Discovery (AViDD) Centers and the Antiviral Program for Pandemics, to include HDA research. This integration would ensure a comprehensive approach to antiviral development.

The recent outbreaks of H5Nx viruses underscore the need for comprehensive antiviral strategies. While DAAs remain a critical component of antiviral therapy, including HDAs offers a promising avenue that can enhance the effectiveness and resilience of our response to viral pandemics. Government funding, particularly through agencies like NIAID and BARDA, is essential to support the research and development of these innovative therapeutics. By

embracing a dual approach that includes both DAAs and HDAs, we can build a more robust and versatile antiviral arsenal to combat current and future viral threats.

Author contributions

DM: Conceptualization, Writing – original draft, Writing – review & editing. RT: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

Author DM was employed by TrippBio Inc.

The remaining author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Available online at: https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON520 (Accessed 12 June 2024).

2. Available online at: https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/h5n1-response-06072024.html:~:text=To%20date%2C%20there%20have%20been,U.S.%20general%20public%20remains%20low (Accessed 12 June 2024).

3. Available online at: https://www.nih.gov/news-events/news-releases/nih-releases-h5n1-influenza-research-agenda:~:text=The%20research%20agenda%20focuses%20on,novel%20treatments%2C%20including%20antivirals%20and (Accessed 12 June 2024).

4. Kiser JJ, Flexner C. Direct-acting antiviral agents for hepatitis C virus infection. *Annu Rev Pharmacol Toxicol.* (2013) 53:427–49. doi: 10.1146/annurev-pharmtox-011112-140254

5. von Delft A, Hall MD, Kwong AD, Purcell LA, Saikatendu KS, Schmitz U, et al. Accelerating antiviral drug discovery: lessons from COVID-19. *Nat Rev Drug Discov.* (2023) 22:585–603. doi: 10.1038/s41573-023-00692-8

6. Tripp RA, Martin DE. Screening drugs for broad-spectrum, host-directed antiviral activity: lessons from the development of probenecid for COVID-19. *Viruses.* (2023) 15:2254. doi: 10.3390/v15112254

7. Sanjuán R, Domingo-Calap P. Mechanisms of viral mutation. *Cell Mol Life Sci.* (2016) 73:4433–48. doi: 10.1007/s00018-016-2299-6

8. Mueller SN, Rouse BT. 27 - Immune responses to viruses. *Clin Immunol.* (2008), 421–31. doi: 10.1016/B978-0-323-04404-2.10027-2

9. Krishnamurthy N, Grimshaw AA, Axson SA, Choe SH, Miller JE. Drug repurposing: a systematic review on root causes, barriers and facilitators. *BMC Health Serv Res.* (2022) 22:970. doi: 10.1186/s12913-022-08272-z