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Targeting the Achilles Heel of Zika Virus and Other Emerging Viral Pathogens

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Viruses are a leading cause of infectious diseases and represent one of the world's biggest global health problems. The continual appearance of new and reemerging viruses exceeds our capacity to provide effective medical solutions, as highlighted by the recent Zika epidemic. Herein, the authors discuss how unconventional approaches might lead to innovations in antiviral drug development that would address this outstanding need. In particular, the case of Zika virus is analyzed and the authors suggest that a materials science and engineering perspective might revolutionize antiviral drug development. Zika virus and related viruses possess a lipid membrane envelope that is an Achilles heel because it is necessary for viral function and there is a high barrier for mutations to evolve there. The development of antiviral drugs, such as certain membrane-active peptides, to selectively target the lipid membrane envelope would represent an entirely new therapeutic approach. Such efforts could be aided by engineering approaches to design and characterize promising drug candidates that work against multiple viruses. Looking forward, there is excellent potential to develop new therapeutic strategies that target the Achilles heel of Zika virus and other emerging viral pathogens.

As the world becomes increasingly connected, the number of emerging and reemerging infectious diseases rises unabated and surpasses our present capabilities to deploy effective antiviral responses. Indeed, as part of a recently published blueprint aimed at preventing future epidemics, the World Health Organization named an unknown disease, referred to as Disease X, as one of the eight potential global disease threats in light of the high risk that a serious epidemic could arise from a currently unknown pathogen.[1]

It is within this context that the recent Zika epidemic represents one of the world's most pressing global health emergencies and highlights the need for innovative approaches to develop effective therapeutic countermeasures.[2,3] While Zika virus has been known for more than half a century, until recently, it was classified as a neglected tropical disease with limited geographical scope and there were few cases of human infection.[4] Then, suddenly, in 2007, a Zika virus outbreak was reported on Micronesia's Yap Island and more than 70% of the population was infected within a matter of months.[5] While this outbreak was the first time that Zika virus infected humans outside of Africa or Asia, efforts to develop Zika countermeasures remained scarce. With Zika infection causing mild symptoms in human patients, targeted drug development against Zika virus was not a priority at the time.

Now, the differences in circumstances could not be more striking. Over the past 3 years, the global spread of Zika virus reached epidemic levels across at least four continents and there is concern about serious clinical symptoms caused by circulating strains, including neurological damage such as Guillain–Barré syndrome[6] and links between Zika infection and the rise of microcephaly among neonates.[7] The pace of the epidemic increased quickly and local transmission of Zika virus even reached nations with advanced healthcare infrastructures such as the United States.[8] Such figures had broad public health consequences like government-promoted suggested efforts to delay pregnancy in certain affected regions.[9] Moreover, there are a number of possible transmission routes including mosquito vectors and human blood-borne and sexual transmission.[10]

Given the pace of viral spread worldwide, the current lack of countermeasures to deal with the Zika epidemic is particularly concerning and represents a major gap in the global health infrastructure. Indeed, there are currently no approved vaccine or therapeutic medicines against Zika infection.[11] It will likely still take at least several years for approval of a Zika vaccine. Meanwhile, there are open discussions about possible therapeutic strategies for thwarting Zika virus infection (**Figure 1**). Direct-acting small molecule drugs typically inhibit viral genome replication, while antibodies and other neutralizing agents target virus particles and prevent infection. Both strategies are attractive yet challenging to implement. Viral genome replication has low fidelity and hence the rise of drug-resistant strains is another major problem. Likewise, antibody-based treatments, such as those being developed for Ebola infection,[12] can take years to develop into clinically viable regimens and production scale-up

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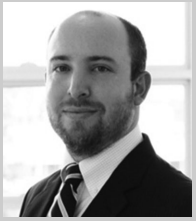

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is challenging. Moreover, the ongoing development of advanced Zika animal models underscores the challenges that lie ahead for even achieving a fundamental understanding of Zika biology that could lead to targeted Zika therapies.[13] Importantly, Zika is not a one-off problem but rather the most recent example of the pattern of viral outbreaks that emerge from unsuspecting sources and, even when predicted in advance, such pathogens are challenging to counter. Addressing this challenge requires unconventional thinking and presents the opportunity to develop innovative antiviral strategies. To achieve this goal, we need a radical rethinking about how we approach antiviral drug development and much can be gained from a materials science and engineering perspective—translating current knowledge about Zika virus into rationally designed therapeutic strategies.

The Zika virus is a member of the *Flaviviridae* family and is a mosquito-borne *Flavivirus* related to the dengue, Yellow Fever, and West Nile viruses.[14] Like other flaviviruses, the Zika virus is an enveloped, positive strand RNA virus and the viral genome encodes structural and nonstructural proteins that are part of new virions and aid viral genome replication, respectively.[15] While the biochemical features of specific viruses can be quite divergent, all flaviviruses constitute infectious virus particles with around 40–55 nm diameter.[16] Recent efforts have identified that the Zika virus falls within this target size range and structural insights suggest that the particles may be susceptible to treatment with structure-destabilizing therapeutic agents.[17,18] Strikingly, newly produced virus particles are surrounded by a lipid bilayer envelope that is derived from infected host cells and this envelope plays important roles in the virus life cycle, including protecting viral genetic material and facilitating cell infection. Hence, hindering the function of the viral lipid envelope is an attractive therapeutic strategy that targets a common element of many medically important viruses, including Zika virus.

To date, both small molecules and peptide drugs have been reported that interfere with or lyse viral envelopes in order

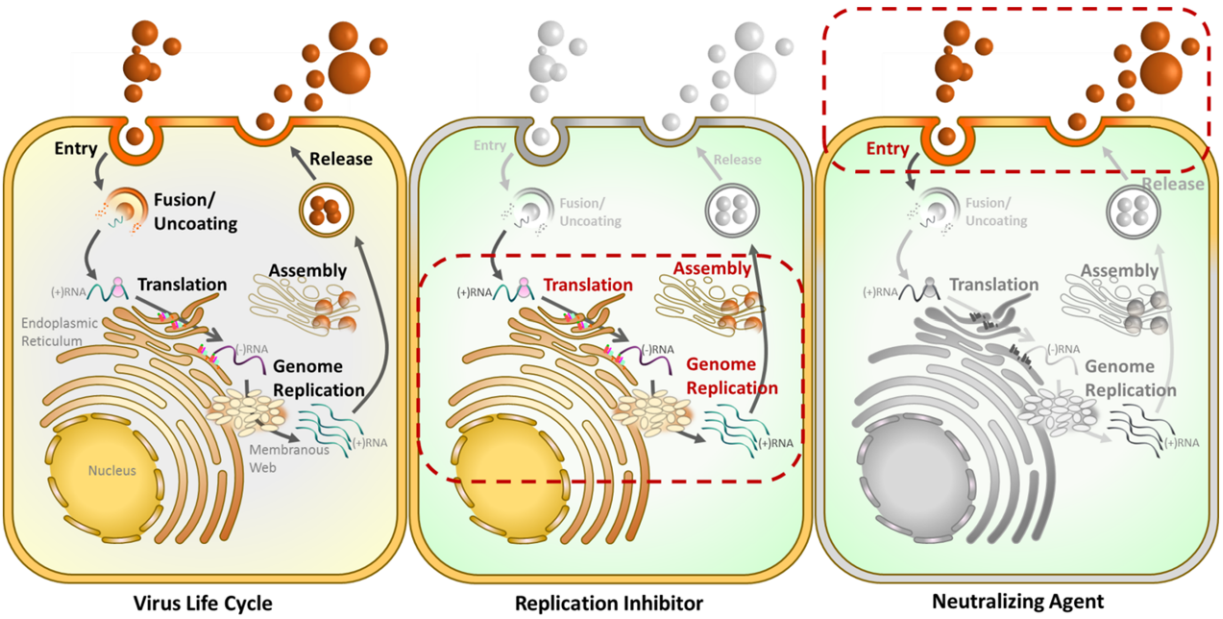

Figure 1. Antiviral strategies for combating Zika virus. The Zika virus life cycle shares common features with other flaviviruses (left). Conventional direct-acting antiviral drugs interfere with replication of the viral genome and stop production of virion progeny (middle). Virus neutralization occurs by directly interfering with virus particles and either blocking infection by intact virions or lysing virions in extracellular space (right). Bolded terms within the images reflect key processes that are targeted by different antiviral strategies.

to blunt virus infectivity.[19] In particular, certain membrane-active peptides have been shown to have highly selective activity against curved lipid membranes such as nanoscale virus envelopes while leaving much larger human cell membranes largely unaffected.[20–22] Exploiting this Achilles heel of Zika virus particles—the viral envelope—holds great potential for rapid development of effective treatment options and our preliminary evidence supports that Zika virus, like other flaviviruses, can be targeted by specific antiviral peptides. Curiously, materials science–based biophysical assays have revealed that such behaviors are exhibited by only a small fraction of membrane-active peptides.[23,24] While so much effort has been placed on membrane-active, antibacterial and antifungal peptides over the past few decades,[25] the field of membrane-active antiviral peptides is just beginning to emerge. There is already a growing number of membrane-active antiviral peptides with demonstrated inhibitory activity in vitro,[26–28] and further exploration of nanomedicine-based strategies[29–31] to increase therapeutic efficacy is an exciting direction for integrating materials science approaches with antiviral medicine. Considering the long-established practice of peptide antibiotics for treatment of bacterial infections,[32] there is strong precedence for exploring the use of antiviral peptides to treat virus infections. Traditionally, peptide therapeutics have been viewed less favorably due to relatively short circulation times and requiring injectable administration (often intravenously or subcutaneously), however, there is extensive ongoing innovation in the development of peptide therapeutics.[33] Promising examples include stapled peptides that can be administered orally[34] and polymer-modified peptides with longer circulation times.[35]

In the present context, antiviral peptides deserve attention alongside small molecules and therapeutic antibodies as a potential treatment option against Zika virus and other emerging viral threats, especially as a possible short-term solution to blunt emerging virus epidemics. The recent Yellow Fever virus outbreak in Brazil is another example of a situation where effective therapeutic interventions would be extremely opportune.[36] Time and time again, crises have driven innovation and the Zika epidemic and other recent viral outbreaks hold the potential to improve antiviral drug development and establish new strategies for the rapid blunting of spreading viruses.

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Conflict of Interest

The authors declare no conflict of interest.

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