Zika and Other Emerging Viruses: Aiming at the Right Target

Kai Dallmeier1 and Johan Neyts1,*

1Rega Institute for Medical Research, Department of Microbiology & Immunology, University of Leuven (KU Leuven), 3000 Leuven, Belgium
*Correspondence: johan.neyts@kuleuven.be

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The Zika emergency calls for urgent countermeasures. Recently, Barrows et al. (2016) and Xu et al. (2016) conducted in vitro anti-ZIKV screens to identify potential therapeutics. The off-label use of drugs that may protect against Zika virus-induced brain damage has, however, to be balanced with their risk during pregnancy.

Emerging and neglected (or in the case of Zika, “forgotten”) viruses claim the scene with an apparently accelerating speed; examples include (but are not limited to) the Hendra virus (1994), the West Nile virus (1999), the SARS and MERS coronaviruses (2002 and 2012), H1N1 pandemic influenza (2009), and the Ebola virus (2014). At the occasion of most outbreaks, authorities announce public health emergencies. Each time neither the scientific community nor the pharmaceutical industry is ready to conquer the problem. Outbreak after outbreak, the world is taken by surprise and left without vaccines or potent antivirals. At the time that a highly pathogenic virus (re-)emerges, years will be needed, if not a decade, before vaccines or drugs will become available, even with accelerated procedures. The recent re-emergence of the Zika virus (ZIKV) is no exception to this. This time, the pathogen hits mostly the most vulnerable, i.e., the human fetus (Lessier et al., 2016). Until safe and efficient ZIKV vaccines become available, mankind is, given the lack of specific antivirals, blunted of any countermeasures to prevent or treat infections with this virus.

In an attempt to bridge this gap, two groups recently conducted an in vitro anti-ZIKV screen using a set of ~800 FDA-approved drugs (Barrows et al., 2016) or, in addition to this collection, another ~5,600 drug-like molecules with known biological activity (Xu et al., 2016). Barrows and colleagues employed an imaging-based approach in which compound-pretreated human hepatoma cells were infected with a ZIKV isolate from the current outbreak. Infected cultures were fixed 24 hr after infection, and the fraction of cells expressing ZIKV antigens was quantified. Using this approach, 24 molecules (hit rate 6%) were reported to inhibit ZIKV replication. The antiviral activity of a smaller subset of hits was confirmed in cells derived from pathophysiologically relevant tissues, such as the CNS and amniotic tissue.

Xu et al. (2016) established their screenings assay based on the previous observation that ZIKV of the African lineage induces activation of effector caspases and subsequent cell death within 4 hr post infection of glioblastoma cells. In an orthogonal screen, 116 hits (hit rate ~2%) were shown to protect human neuronal progenitor cells against the virus. The activity of 35 of these molecules was confirmed in three different cell lines, including astrocytes. This set of 35 inhibitors was divided into (i) those that affect ZIKV replication or (ii) agents that protect infected cells from death.

Among their 24 hits, the Barrow team identified mycophenolic acid (MPA, the active component of the immunosuppressive drug Cellcept), the antiparasitic drug ivermectin (which we reported earlier to inhibit in vitro flavivirus replication; Mas trangelo et al., 2012), and mefloquine, an inhibitor of autophagy. Other molecules identified in this study were antibiotics with an unknown mechanism of action (such as dapomycin), the proteasome inhibitor bortezomib, and the antidepressant sertraline. Some of these drugs affect nucleoside metabolism (MPA depletes dGTP and GTP pools), DNA synthesis, and cellular signaling. Such molecules may serve as good chemical probes to aid in understanding the biology of ZIKV replication (Figure 1). The observed effects were already quantified 24 hr after infection, a timespan during which roughly one to two full viral replication cycles can take place. Typically longer assays allow for a more stringent measure of potential antiviral activity and selectivity. For almost all molecules, the in vitro antiviral activity was accompanied with a marked cell loss (Barrows et al., 2016), pointing toward rather non-selective antiviral effects. Molecules that exhibited the most pronounced activity in these assays, such as MPA and bortezomib, belong to pregnancy category D drugs that are strictly contraindicated. Furthermore, it is also reasonable to assume that treatment with the immunosuppressive drug MPA may prolong, rather than shorten, virus persistence (Driggers et al., 2016). Moreover, depending on the concentration that was used, a compound such as the antibiotic daptomycin also resulted in an unwanted, proviral effect.

Xu et al. (2016) identified, possibly biased by their initial caspase reporter readout, the pan caspase-inhibitor emricasan as an agent that protects against ZIKV-induced apoptosis. Whereas emricasan was found not to interfere with viral replication, several inhibitors of cyclin-dependent kinases (CDKi) suppressed the expression of ZIKV proteins and viral progeny production (Figure 1). The most pronounced effect was observed with seliciclib, a known inducer of apoptosis. Another antihelmintic drug, namely niclosamide, was shown to inhibit ZIKV infection. Auspiciously, the combination of emricasan (protecting against cell death) and niclosamide (inhibiting viral replication) or a CDKi reduced both the number of infected cells and the number of cells undergoing concomitant cell death. Among these, at least niclosamide is not precluded during pregnancy.

Intriguingly, but also of concern, is that both screens, though using the same library of FDA-approved drugs, do not
INHIBITION OF ZIKV REPLICATION

Figure 1. Repurposing of Licensed Drugs and Drug-like Small Molecules to Prevent and Treat ZIKV Infections

In two drug repurposing screens, a small selection of FDA-approved drugs and other biologically active compounds proved (i) to inhibit in vitro ZIKV replication or (ii) to protect infected cells from death. While many of these hits are strictly contraindicated during (early) gravidity, at least daptomycin and niclosamide are not precluded from use in pregnant women.

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REFERENCES


