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Hot Topic

Fighting viruses with antibiotics: an overlooked path

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Viruses are a serious threat for humans worldwide because there are in their ranks many causative agents of potentially fatal infections and cancers [1,2]. Despite this, emerging or re-emerging viral infections recurrently demonstrate the absence of efficient antivirals for their prevention, control and cure. This has been successively exemplified in the 21st century by the shortage of antiviral therapies for SARS-CoV (severe acute respiratory syndrome coronavirus), MERS-CoV (Middle East respiratory syndrome coronavirus), Chikungunya virus, Ebola virus and Zika virus [3,4]. In addition, we are insufficiently powerful against some older viral foes. For instance, although the success of drugs discovered for human immunodeficiency virus (HIV), one of 'the big three' worldwide killers, and hepatitis B virus is beyond doubt, these compounds can only control replication, not cure people of these viral infections [5,6]. Thus, overall, the paths towards efficient antiviral therapies have been far less fruitful than for bacteria. Certainly, particular features of the virus lifestyle, among which are intracellular replication, association with the cell machinery, high replication and mutation rates, integration into the host DNA and limited drug access to reservoirs, may explain this difference [7–9]. However, if we think more broadly, we can observe that drug discovery has followed different routes for bacteria and viruses.

With regard to bacteria, it appeared from the serendipitous discovery in 1928 of penicillin secreted by a fungus [10] that using the armamentarium developed by microbes to fight each other was a valuable strategy. Thus, most of the modern antibiotic classes have emerged between the 1940s and 1970s through screening and then modifying molecules originating from bacteria such as *Streptomyces* and related actinomycetes, or fungi such as *Penicillium*, *Cephalosporium*, *Saccharomyces* and *Aspergillus* [11]. Despite its tremendous contribution, this strategy did not cross the border between disciplines in infectious diseases to be applied to viruses. This likely relates partly to the fact that studies of microbes and viruses have been partitioned for a long time. Thus, from the very onset of the history of virology in the 1890s, viruses were understood as differing from microbes owing to their ultrafilterability and their invisibility under a light microscope [12,13]. Then, the concept of virus was eventually defined during the 1950s with criteria that definitively separated viruses from microbes [12,14]. Since then, bacteriology and virology increasingly became two different fields explored by different biologists and researchers. Hence, the crossover of knowledge and transversality of approaches have been considerably hampered. Even now, with the advent of metagenomics, the microbiota and the virome are usually studied separately and by different teams. For instance, among publications retrieved from the ISI Web of Science using virus or bacteria independently as keywords, only ca. 3–4% are still found when using both terms concurrently.

Three recent articles in 2016 have described that compounds of bacterial origin could inhibit the replication of viruses in vitro [15–17] (Table 1). Wang et al and Zhou et al observed that teicoplanin, a semi-synthetic glycopeptide used in the clinic for its activity against Gram-positive bacteria, could inhibit Ebola envelope pseudotyped viruses [15,16]. Teicoplanin is a complex of fermentation products originating from *Actinoplanes teichomyceticus*, an *Actinobacteria* member, and exerts its bactericidal effect through inhibition of bacterial cell wall biosynthesis. In their work, Wang et al used pseudotyped Ebola viruses containing a luciferase reporter gene to screen 1280 U.S. Food and Drug Administration (FDA)-approved compounds [15]. They detected that teicoplanin significantly inhibited Vero cell infection by pseudotyped Ebola viruses. Wang et al noted that teicoplanin had already been reported as active against other enveloped viruses [15]. They further observed that this drug was inactive against three picornaviruses, which are non-enveloped viruses, and that it did not inhibit the pseudotyped Ebola virus when tested after viral adsorption to the cell surface. Taken together, these data suggested that teicoplanin blocks the viral entry step. In a second study, Zhou et al tested 1600 FDA-approved drugs and also observed that teicoplanin inhibited HEK293T cell infection by pseudotyped Ebola viruses [16]. This team further found evidence that the teicoplanin target was located on the host cells and was cathepsin L, which performs glycoprotein proteolysis required for membrane fusion during the entry step of Ebola viruses and SARS-CoV. Finally, other teicoplanin and glycopeptide antibiotics, including dalbavancin, oritavancin and telavancin, but not vancomycin, were found to inhibit the entry of Ebola virus, SARS-CoV and MERS-CoV transcription- and replication-competent virus-like particles. In a third study, Varghese et al identified that ivermectin and abamectin were active on Chikungunya virus [17]. Both drugs derive from avermectin, which is produced by the bacterium *Streptomyces avermitilis* and whose

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Table 1
Main findings of recent studies on the antiviral activity of teicoplanin and ivermectin.

References	Targeted virus	No. of compounds tested	Compound with antiviral activity	System used for antiviral activity screening	50% Effective concentration (EC_{50})[a]	Activity on other viruses
[15]	Ebola virus	1280 (FDA-approved drugs)	Teicoplanin	Ebola virus glycoprotein/HIV core pseudovirus replication on Vero cells	2.38 μM	Human respiratory syncytial virus
[16]	Ebola virus	1600 (FDA-approved drugs)	Teicoplanin	Envelope pseudotyped virus replication on HEK293T cells; viral entry inhibition on primary human umbilical vein endothelial cells, A549 cells and HeLa cells	0.34 μM	Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV)
[18]	Flaviviruses: dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, murine flavivirus Modoc virus	1	Aglycone analogue of teicoplanin	Cytopathic effect reduction assay on Vero-B or BHK-21 cells; BHK-21 cells harbouring the subgenomic dengue virus replicon system	Between 0.3 ± 0.2 μM and 13 ± 4.9 μM	–
[19]	Coronaviruses: SARS-CoV and feline infectious peritonitis virus (FIPV)	ca. 180	Modified glycopeptide derivatives including teicoplanin derivatives	Vero E6 (SARS-CoV) and CRFK (FIPV) cells	Between 5.4 ± 3.1 μM and 64 ± 10 μM for SARS-CoV and 1.6 ± 0.3 μM and 62 ± 29 μM for FIPV	HIV-1 (T lymphoblastoid cell line CEM)
[20]	Influenza virus	18	Teicoplanin aglycone derivatives	Influenza A/H1N1, A/H3N2 and B virus strains on MDCK cells (cytopathic effect)	Between 0.15 μM and 100 μM	–
[21]	Influenza virus	13	Saccharide-based versatile lipophilic derivatisation of teicoplanin pseudoaglycone	Influenza A/H1N1 and A/H3N2 virus strains on MDCK cells (cytopathic effect)	Between 0.8 μM and 2.3 μM	–
[22]	Influenza virus	11	Teicoplanin pseudoaglycone derivatives	Influenza A/H1N1, A/H3N2 and B virus strains on MDCK cells (cytopathic effect)	Between 0.54 μM and 23 μM	Herpes simplex virus 1 and 2, vaccinia virus, vesicular stomatitis virus
[23]	HIV	–	Teicoplanin aglycone derivatives	HIV-1 and HIV-2 on various cell lines	Between 2.8 μM and 17 μM	–
[24]	HIV types 1 and 2; Moloney murine sarcoma virus (MSV)	59	Teicoplanin-type aglycones and their derivatives	Cytopathic effect of HIV-1/2 on T lymphoblastoid cell line CEM; transforming effect of MSV on murine C3H/3T3 embryo fibroblast cell cultures	Between 0.75 ± 0.07 μM and 80 ± 28 μM for HIV-1; between 3.0 ± 1.4 μM and 190 ± 84 μM for HIV-2; between 2.0 ± 1.2 μM and 82 ± 26 μM for MSV	–
[25]	Hepatitis C virus (HCV)	–	Teicoplanin	Case report: 1600 mg intravenously 2–3 times a week for a total of 10 weeks (trough level, 9.2–19.9 mg/L)	–	–
[26]	Hepatitis C virus (HCV)	ca. 7000 small molecules containing semisynthetic derivatives of teicoplanin, eremomycin and vancomycin	Teicoplanin aglycone derivatives	Subgenomic HCV replicons	Between 2.9 ± 0.7 μM and 54 ± 12 μM	–
[17]	Chikungunya virus	2933 (clinically approved and non-approved drugs)	Ivermectin	Chikungunya virus-replicon BHK-21 cell line-based assay; inhibition assays with BHK-21 and Huh-7.5 cells	Between 0.6 ± 0.1 μM and 1.9 ± 0.8 μM in BHK-21 and Huh-7.5 cells, respectively	Other alphaviruses: yellow fever virus, Semliki Forest virus, Sindbis virus
[27]	Yellow fever virus (YFV)	1	Ivermectin	Virus yield reduction assays on Vero-B (YFV, DENV) or Vero E6 cells (JEV, TBEV); in vitro helicase/enzymatic assays	Between 0.0031 μM and 0.006 μM (YFV); 0.7 μM (DENV); ca. 0.2 μM (TBEV); 0.3 μM (JEV); 4 μM (WNV)	Dengue fever virus (DENV), tick-borne encephalitis virus (TBEV), Japanese encephalitis virus (JEV), West Nile virus (WNV)
[28]	Porcine reproductive and respiratory syndrome virus (PRRSV)	1	Ivermectin	Replication on porcine alveolar macrophages transfected with CD163 cDNA	6.7 μM; >5 log reduction of the PRRSV titre with 15 μM ivermectin	–
[29]	Dengue virus (DENV)	1 (ivermectin loaded or not in liposomal systems)	Ivermectin	Replication of DENV type 1, 2 and mouse-adapted type 2 strains on Huh-7 cells	Between 2.6 μM and 3.7 μM for ivermectin and between 0.3 μM and 2.7 μM for ivermectin-loaded liposomal formulations	–

FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; HEK, human embryonic kidney; BHK, baby hamster kidney; MDCK, Madin–Darby canine kidney; Huh, human hepatocellular.
[a] EC_{50} values shown are those found as associated with antiviral activity.

discovery was awarded the Nobel Prize in Medicine in 2015 [30]. Ivermectin and abamectin are macrocyclic lactones with a well-known broad activity spectrum against parasites. Ivermectin is widely used in human and veterinary medicine, whereas abamectin is used on agricultural crops. Varghese et al used a fully automated chikungunya-replicon cell line-based assay to screen a panel of 2933 compounds, which included clinically approved drugs as well as drugs in clinical trials [17]. They found that ivermectin and abamectin inhibited chikungunya virus replication in a dose-dependent manner and decreased the synthesis of genomic RNA, antigenomic RNA and proteins from this virus. In addition, these drugs were also efficient against Semliki Forest virus and Sindbis virus, two other alphaviruses, and on yellow fever virus, a flavivirus, suggesting broad antiviral activity. These three articles are the most recent examples of reports on the antiviral activity of drugs of bacterial origin. Previously, teicoplanin had already been reported as active against HIV, hepatitis C virus, flaviviruses, coronaviruses, respiratory syncytial virus and influenza virus [15]. In addition, ivermectin had been previously shown to inhibit the NS3 helicase of three flaviviruses, namely yellow fever virus, dengue virus and West Nile virus [27] (Table 1). Among other examples of drugs of bacterial origin that are active against viruses, previous works showed the activity of valinomycin, a cyclododecadepsipeptide produced by *Streptomyces*, against the SARS-CoV [31], and of a bacteriocin produced by *Enterococcus faecium* against herpes simplex virus [32].

These findings make biological sense. Viruses are currently considered to be the most abundant biological entities on Earth and are estimated to outnumber bacteria and eukaryotes by 1–2 $\log_{10}$, respectively, and viral diversity appears to be tremendous and still largely untapped [33]. Moreover, recent technological advances that include high-throughput sequencing, metagenomics and culturomics have emphasised the concurrent presence in environmental samples, as well as in humans, of viruses, bacteria, archaea and eukaryotes [34–38]. This indicates that bacteria may not only compete and fight among each other, but also with multiple viruses. Among viruses there are well-known bacteria killers, bacteriophages, which have a major impact on environmental bacterial communities [39] and have been proposed for treating bacterial infections in humans [40]. Conversely, during the past decade, CRISPR have been discovered in bacteria as an amazing mechanism of adaptive immunity against invading viruses, demonstrating that the war is bilateral [41]. Therefore, it can be hypothesised that bacteria could have developed, concurrently with antibiotics, antivirals. Nonetheless, whilst the fact that microbes interact and fight among each other has been in the forefront for decades in bacteriology, their capability to threaten viral replication has been widely overlooked [9].

The studies by Wang et al [15], Zhou et al [16] and Varghese et al [17] are only the first steps towards a possible use of antibiotics and antiparasitic drugs derived from bacteria as antivirals, which may represent another example of the benefits of drug repurposing [42,43]. Their results have to be confirmed, and it has to be determined whether concentrations within the therapeutic range can be achieved to target viruses. Nonetheless, these studies highlight that the potential antiviral activity of antimicrobials may be untapped. Another lesson from these articles regards the strategy chosen to discover drugs with an antiviral effect. Indeed, no hypothesis, prediction or modelling has been made. In contrast, the strategy was straightforward and consisted of massive high-throughput screening of hundreds or thousands of available drugs, regardless of their known activity spectrum and target or their approved indication. This is a different approach than specifically targeting stages of the virus replication cycle through blocking proteins involved in their progress [44]. In addition, aside from the great interest in approved drugs for the potential treatment of viral infections for which we currently lack antivirals, we usually have, as is the case here for teicoplanin and ivermectin, considerable experience with their use in humans, which could accelerate their access to the clinic.

In summary, these recent findings open wide a new field in the fight against viral infections. They highlight the fact that research in bacteriology and virology should not be tightly compartmentalised, and they show that, as has been done for antibiotics and in various other fields [4,45,46], mimicking the living is probably a valuable strategy in improving and expanding our antiviral armamentarium.

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