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Short communication

Teicoplanin inhibits Ebola pseudovirus infection in cell culture

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ABSTRACT

There is currently no approved antiviral therapy for treatment of Ebola virus disease. To discover readily available approved drugs that can be rapidly repurposed for treatment of Ebola virus infections, we screened 1280 FDA-approved drugs and identified glycopeptide antibiotic teicoplanin inhibiting Ebola pseudovirus infection by blocking virus entry in the low micromolar range. Teicoplanin could be evaluated further and incorporated into ongoing clinical studies.

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Ebola virus (EBOV), a member of the Filoviridae, is an enveloped, filamentous, non-segmented negative-sense RNA virus that can cause deadly Ebola virus disease (EVD) (Feldmann and Geisbert, 2011). In February 2014, the largest known EVD outbreak started in Guinea, and virologic investigation identified Zaire ebola virus (ZEOBV) as the causative agent (Baize et al., 2014). As of 26 July 2015, a total of 27,784 cases and 11,294 deaths were reported (http://www.who.int/csr/disease/ebola/situation-reports/en/), resulting in a fatality rate of 40.6%. To date, no antiviral or therapeutic has been approved for treating patients with EVD, and treatment remains limited to supportive care. Therefore there is an urgent need for the discovery and development of antiviral agents against EBOV infection.

EBOV is a biosafety level 4 (BSL-4) pathogen and work with infectious EBOV is restricted to only a few BSL-4 laboratories. Hence the biology of EBOV infection remains relatively poorly understood hampering vaccine and drug development. In order to overcome this limitation, surrogate systems which allow modeling of the virus life cycle under BSL-2 conditions have been developed (Hoenen and Feldmann, 2014). Pseudoparticles expressing EBOV glycoprotein (GP) is the most commonly used tool for the study of EBOV entry and identification of EBOV entry inhibitors. Virus attachment and entry offer numerous targets for antiviral therapy and T20 (enfuvirtide), a peptide inhibitor of gp41-mediated virus entry has been successfully used in the treatment of HIV-1 infection (Altmeyer, 2004). We set out to screen approved drugs for identification of potential therapeutic options for EVD. Drug repurposing is a valid approach, and several existing drugs have been proven to be effective in the new indications (Ashburn and Thor, 2004; Chong and Sullivan, 2007).

We performed a screen of 1280 FDA-approved drugs using EBOV (Zaire strain) GP/HIV core pseudovirus containing firefly luciferase (FLuc) reporter gene (designated as pEBOV, kindly provided by Prof. Paul Zhou from Institut Pasteur of Shanghai) to identify new inhibitors. Fig. 1A shows the scheme of primary screening and hits selection process. Briefly, Vero cells (10,000 cells in 50 µl of DMEM) were seeded into each well of a white 96-well plate (Corning Costar) and incubated at 37 °C with 5% CO2 for 24 h prior to infection. Five microliters of each test compound at a final concentration of 10 µM (diluted in assay media with a final DMSO concentration of 0.25%) were added to the plates (one compound per well). In cell control and pEBOV infection control wells, 0.25% DMSO alone was added. Within 10 min of compound addition, 45 µl
of 1:20-diluted pEBOV was added to each well. In cell control wells, 45 µl of assay medium was added. The final assay volume was 100 µl/well. Plates were then incubated at 37 °C with 5% CO₂ for 72 h and allowed to equilibrate to room temperature for 30 min. Afterward, 50 µl of Bright-Glo (Promega) reagent was added to each plate well, and the plates were incubated at room temperature for

Fig. 1. Identification of teicoplanin as an inhibitor of EBOV pseudovirus (pEBOV). (A) Flowchart of screening procedure. 1280 compounds from the FDA-approved compound library were screened in single dose at 10 µM for activity against pEBOV. 137 compounds that had activity (>50% inhibition) against pEBOV were subsequently screened against VSV pseudovirus (pVSV), leading to 15 compounds that were selectively active against pEBOV. Dose-response analysis confirmed that two compounds (teicoplanin and toremiphene) met the selection criteria of EC₅₀ < 10 µM, SI > 10 against pEBOV, and pEBOV/pVSV > 10. (B) Activity of teicoplanin against pEBOV and pVSV. Three-fold serial dilutions of teicoplanin were added to Vero cells, after 72 h of incubation, the relative infectivities were analyzed by measuring the luciferase and presented as a percentage of luciferase derived from the compound-treated cells compared with that from the mock-treated cells. Cytotoxicity was also examined by incubation of Vero cells with the indicated concentrations of teicoplanin and was presented as a percentage of luminescence derived from the compound-treated cells compared with that from the mock-treated cells (with medium). (C) Effect of human serum albumin (HSA) on the anti-pEBOV activity of teicoplanin. Activity of teicoplanin against pEBOV was evaluated in the presence of indicated concentrations of HSA and EC₅₀ were calculated using Prisim’s nonlinear regression (GraphPadPrism5). (D) Activity of vancomycin against pEBOV. Left, chemical structure of vancomycin; right, activity of vancomycin against pEBOV and cytotoxicity of vancomycin. For (B), (C), and (D), average results from three experiments are shown. Error bars represent the standard deviations (B and D) or standard error (C) of means of three independent measurements.
Table 1
Compounds with activity against EBOV pseudovirus.

| Name                | CC50 (μM) | EC50 (μM) | SI pEBOV/pVSV | pEBOV  | pVSV  |
|---------------------|-----------|-----------|---------------|--------|-------|
| Teicoplanin         | >125      | 2.38      | >125          | >52.52 | N.D   |
| Tamoxifen           | 10.09     | 0.75      | 4.94          | 13.47  | 2.04  | 6.59 |
| Clemastine          | 15.80     | 3.01      | 10.31         | 5.25   | 1.53  | 3.43 |
| Toremiphene         | 10.16     | 0.38      | 7.53          | 26.73  | 1.35  | 19.82|
| Paroxetine          | 18.10     | 2.40      | 7.39          | 7.54   | 2.45  | 3.08 |
| Amiodarone          | 54.18     | 4.03      | 8.18          | 13.44  | 6.62  | 2.03 |
| Clomiphene          | 15.30     | 1.83      | 8.17          | 8.36   | 1.87  | 4.46 |
| Securinine          | 113.58    | 27.11     | 26.64         | 4.19   | 4.26  | 0.98 |
| Glafenine           | >100      | 11.13     | 10.89         | >8.98  | >9.18 | 0.98 |
| Oxeladin            | >100      | 8.06      | 38.08         | >12.41 | >2.63 | 4.72 |
| Pimethixene maleate | 19.76     | 10.66     | 14.83         | 1.85   | 1.33  | 1.39 |
| Artemisinin         | >500      | 74.14     | 161.60        | >6.74  | >3.09 | 2.18 |

(continued on next page)
with an EC50 of 2.38 \( \mu \text{M} \) (Wilson, 2000; Yagasaki et al., 2003), we evaluated the effect of human serum albumin (HSA) on the anti-pEBOV activity of teicoplanin. In the presence of HSA, the dose-response curves shifted toward higher EC50 values as the concentration increased (Fig. 1C). The fold shift in EC50 was 5.4, 6.0, and 7.3 in the presence of 1%, 3%, and 5% HSA, respectively. As albumin is present in human serum at concentrations in the range of 35–45 mg/ml, the EC50 of teicoplanin against pEBOV in humans should be in the range of 12.03–14.56 \( \mu \text{M} \) (20.56–24.89 mg/L). Recently, Johansen and coworkers (Johansen et al., 2015) also showed that teicoplanin is active against eGFP-EBOV in vitro, however, no protection was observed in EBOV-infected C57BL/6 mice after treatment with teicoplanin at a dose of 14 mg/kg of body weight once daily for 10 days. We speculate that the failure was due to the therapeutic concentration of teicoplanin not being achieved. Perhaps a higher dose e.g. daily dose of 40 mg/kg that has shown to be safe and effectively in decreasing bacteremia (Domenech et al., 2004) may lead to significant survival benefits. To maintain serum concentration of teicoplanin above the EC50 in patients infected with EBOV is the key to successful outcome in clinical settings. Given that a trough plasma concentration (Cmin) of 20–60 mg/L (>the estimated EC50 against pEBOV in human) is achieved in 30–70% samples and toxicity is not seen until Cmin reach 60 mg/L (Tobin et al., 2010), teicoplanin may be of potential for treatment of EVD. Nevertheless, new dosage guidelines should be developed to ensure optimal drug exposure for the majority of patients who may have EVD. Moreover, vancomycin which is also used for the treatment of gram-positive bacterial infections and structurally related to teicoplanin only showed 24.7% inhibition at 125 \( \mu \text{M} \) (Fig. 1D), suggesting the structural difference between teicoplanin and vancomycin, e.g. a long fatty acid chain attached to teicoplanin that is absent in vancomycin and different structures of their aglycones is crucial for anti-pEBOV activity.

EBOV binds to target cells through interactions of either glycans on GP with C-type lectins (CLECs) or virion-associated phosphatidylycerine with phosphatidylycerine receptors to initiate entry (Moller-Tank and Maury, 2015), after which it is internalized via macropinocytosis and traffics to the endosomes (Sanbo et al., 2010; Saeed et al., 2010), where GP is cleaved by host proteases such as cathepsins (Chandran et al., 2005). Binding of cleaved GP to the endosomal membrane protein Niemann-Pick C1 (NPC1) triggers fusion and facilitates the release of the viral nucleoprotein into the cytoplasm prior to the initiation of virus replication (Carette et al., 2011; Cote et al., 2011). To determine the stage of the viral entry

| Name       | Structure | CC50 (\( \mu \text{M} \)) | EC50 (\( \mu \text{M} \)) | CC50/EC50 | EC50/pVSV | SI pEBOV/pVSV |
|------------|-----------|---------------------------|--------------------------|-----------|-----------|---------------|
| Indoprofen | ![Indoprofen](image1.png) | 91.85 | 9.37 | 8.51 | 9.80 | 10.79 | 0.91 |
| Idoquinol  | ![Iodoquinol](image2.png) | 16.64 | 3.50 | 3.45 | 4.75 | 4.82 | 0.99 |
| Levonordefrin | ![Levonordefrin](image3.png) | >50 | >50 | >50 | N.D | N.D | N.D |

* \( \text{pEBOV/pVSV} = \frac{\text{EC50 of pVSV}}{\text{EC50 of pEBOV}} \), N.D, not determined.
The minigenome system (schemed in Fig. 2B, and all constructs were synthesized by Generay Biotech Ltd, Shanghai, China based on the sequences of GenBank accession number AY354458) to test whether teicoplanin inhibits EBOV replication. BSR T7/5 cells stably expressing the T7 RNA polymerase (kindly provided by Prof. Dr. Karl-Klaus Conzelmann from Max-von-Pettenkofer Institut, Germany) were seeded at 2 x 10^5 cells/well in a 24-well plate (Corning Costar) 24 h in advance. Cells were transfected with plasmids encoding for EBOV NP (100 ng), VP35 (100 ng), VP30 (60 ng), L (600 ng) proteins, and minigenome (50 ng) containing the Fluc reporter gene using Lipofectamine 2000 (Invitrogen). Plasmid pRL-SV40 (5 ng) encoding renilla luciferase was co-transfected as an internal control to normalize transfection efficiency, and transfection without plasmid expressing L protein served as negative control. Teicoplanin was added after transfection, and left to incubate with the cells. After 24 h of transfection, cells were lysed in luciferase lysis buffer and firefly luciferase as well as renilla luciferase signals were measured for each well with dual-luciferase reporter assay system (Promega). In contrast to inhibitory effects on subgenomic HCV replication, teicoplanin did not inhibit replication of the EBOV minigenome at all tested concentrations (Fig. 2B). This observation together with the results of pre- and post-attachment assays suggest that the mechanism of inhibition of pEBOV by teicoplanin is by blocking virus entry.

Teicoplanin and its derivatives have been reported to inhibit several viruses such as HIV (Balzarini et al., 2003; Preobrazhenskaya and Olsufyeva, 2006), influenza (Bereczki et al., 2014), HCV (Maieron and Kerschner, 2012; Obeid et al., 2011), dengue virus and other flaviviruses (De Burghgraewe et al., 2012), and coronaviruses including SARS-CoV and FIPV (Balzarini et al., 2006). Because all of these viruses are enveloped viruses, we questioned whether teicoplanin inhibits a wide variety of enveloped viruses but not nonenveloped viruses. We then evaluated the activity of teicoplanin against another enveloped virus human respiratory syncytial virus (hRSV, strain Long) and three non-enveloped viruses including enterovirus 71 (EV-A71, strain Sabin) and poliovirus 1 (PV1, strain Sabin). Interestingly, teicoplanin reduced viral titers of hRSV by 1.8- and 9.4-fold at 30 and 100 mM, respectively (Fig. 3A), however, no inhibition was observed against EV-A71, CV-A16, or PV1 at all tested concentrations (Fig. 3B), suggesting teicoplanin probably targets a common component among those enveloped viruses or target cells.

In conclusion, we identified glycopeptide antibiotic teicoplanin as an inhibitor of EBOV pseudovirus in cell culture by blocking pathway at which teicoplanin inhibits infection, we performed pre- and post-attachment assays. Teicoplanin was incubated with pEBOV for 1 h before or after pEBOV binding to a monolayer of Vero cells, and infection was measured by firefly luciferase assay. As shown in Fig. 2A, teicoplanin efficiently inhibited infection when premixed with pEBOV or added during infection. However, no inhibition was detected when added after virus adsorption to the cell surface, indicating that teicoplanin blocks viral entry. Because teicoplanin aglycone derivatives were reported to inhibit subgenomic HCV replication (Obeid et al., 2011), we took advantage of an EBOV minigenome system (schemed in Fig. 2B, and all constructs were synthesized by General Biotech Ltd, Shanghai, China based on the sequences of GenBank accession number AY354458) to test whether teicoplanin inhibits EBOV replication.

Fig. 2. Teicoplanin blocks pEBOV entry but does not inhibit viral RNA replication. (A) Time-of-addition studies with teicoplanin. Vero cells were infected with pEBOV at 37 °C for 1 h in the presence (during infection) of 10 or 100 μM of teicoplanin and washed to remove unbound pEBOV and compounds, and then fresh medium was added and incubated at 37 °C for 72 h. For the pre-attachment assay, pEBOV was incubated with 10 or 100 μM of teicoplanin at 4 °C for 1 h prior to addition to cells. The virus-compound mixture was incubated with cells at 37 °C for 1 h, after which the cells were washed with medium and incubated at 37 °C for 72 h. For the post-attachment assay, Vero cells were prechilled to 4 °C, and pEBOV was added to cells, and virus adsorption was allowed for 1 h at 4 °C. Cells were washed three times with cold medium to remove unbound virus, and 10 or 100 μM of teicoplanin were added for 1 h at 4 °C, and cells then were washed and incubated at 37 °C for 72 h. The data are the averages for quadruplicate wells for two independent experiments, and the error bars represent the standard deviations of the means. Statistical significance between treated and control group was analyzed by t-test (ns, not significant, *, p < 0.05, **, p < 0.01 ***; p < 0.001). (B) Minigenome assay with teicoplanin. Upper, schematic diagram of the Ebola virus (Zaire strain) minigenome used in this study, in which the viral genes are removed and replaced with a firefly luciferase (Fluc) reporter gene, but the nontranscribed leader and trailer regions as well as the noncoding regions upstream and downstream of NP gene are retained. The minigenome (mg) was flanked by the T7 RNA polymerase promoter (T7) and a ribozyme (HDV). The minigenome is replicated and transcribed by NP, VP35, VP30, and L provided in trans from expression plasmids. Lower, BSR T7/5 cells were transfected with minigenome and expression plasmids for the RNP proteins NP, VP35, VP30, and L, and after 2 h of incubation with transfection complex, cells were treated with 10 μM, 30 μM, or 100 μM of teicoplanin. Firefly and renilla luciferase activities were measured at 24 h post-transfection. Cells transfected without L plasmid were set as background. The effects of teicoplanin were presented as a percentage of firefly luciferase (normalized against renilla luciferase) derived from the compound-treated cells compared with that from the mock-treated cells. The data presented were obtained from two independent experiments. Error bars represent the standard deviations from two independent experiments.
entry. Based on its long history of clinical use and achievable high enough human exposure, teicoplanin has the potential to be rapidly advanced to clinical settings. Moreover, teicoplanin also provides a good tool to gain novel insights into the entry process of EBOV.

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