Eastern equine encephalitis

Eastern equine encephalitis (EEE), commonly called Triple E or, sleeping sickness (not to be confused with trypanosomiasis) is a zoonotic alphavirus and arbovirus present in North, Central, and South America and the Caribbean. EEE was first recognized in Massachusetts, United States, in 1831 when 75 horses died mysteriously of viral encephalitis. Epizootics in horses have continued to occur regularly in the United States. It can also be identified in asses and zebras. Due to the rarity of the disease, its occurrence can cause economic impact in relation to the loss of horses and poultry.

Neurotropic alphaviruses, including western, eastern, and Venezuelan equine encephalitis viruses, cause serious and potentially fatal central nervous system infections in humans for which no currently approved therapies exist. We previously identified a series of thieno[3,2-b]pyrrole derivatives as novel inhibitors of neurotropic alphavirus replication, using a cell-based phenotypic assay (W. Peng et al., J. Infect. Dis. 199:950-957, 2009, doi:http://dx.doi.org/10.1086/597275), and subsequently developed second- and third-generation indole-2-carboxamide derivatives with improved potency, solubility, and metabolic stability (J. A. Sindac et al., J. Med. Chem. 55:3535-3545, 2012, doi:http://dx.doi.org/10.1021/jm300214e; J. A. Sindac et al., J. Med. Chem. 56:9222-9241, 2013, http://dx.doi.org/10.1021/jm401330r). In this report, we describe the antiviral activity of the most promising third-generation lead compound, CCG205432, and closely related analogs CCG206381 and CCG209023. These compounds have half-maximal inhibitory concentrations of ~1 μM and selectivity indices of >100 in cell-based assays using western equine encephalitis virus replicons. Furthermore, CCG205432 retains similar potency against fully infectious virus in cultured human neuronal cells. These compounds show broad inhibitory activity against a range of RNA viruses in culture, including members of the Togaviridae, Bunyaviridae, Picornaviridae, and Paramyxoviridae families. Although their exact molecular target remains unknown, mechanism-of-action studies reveal that these novel indole-based compounds target a host factor that modulates cap-dependent translation. Finally, we demonstrate that both CCG205432 and CCG209023 dampen clinical disease severity and enhance survival of mice given a lethal western equine encephalitis virus challenge. These studies demonstrate that indole-2-carboxamide compounds are viable candidates for continued preclinical development as inhibitors of neurotropic alphaviruses and, potentially, of other RNA viruses. IMPORTANCE There are currently no approved drugs to treat infections with alphaviruses. We previously identified a novel series of compounds with activity against these potentially devastating pathogens (J. A. Sindac et al., J. Med. Chem. 55:3535-3545, 2012, doi:http://dx.doi.org/10.1021/jm300214e; W. Peng et al., J. Infect. Dis. 199:950-957, 2009, doi:http://dx.doi.org/10.1086/597275; J. A. Sindac et al., J. Med. Chem. 56:9222-9241, 2013, http://dx.doi.org/10.1021/jm401330r). We have now produced third-generation compounds with enhanced potency, and this manuscript provides detailed information on the antiviral activity of these advanced-generation compounds, including activity in an animal model. The results of this study represent a notable achievement in the continued development of this novel class of antiviral inhibitors [1)].

In fall 2017, three solid organ transplant recipients from a common donor developed encephalitis within one week of transplantation, prompting suspicion of transplant-transmitted infection. Eastern equine encephalitis virus (EEEV) infection was identified during testing of endomyocardial tissue from the heart recipient.

METHODS: We reviewed medical records of the organ donor and transplant recipients and tested serum, whole blood, cerebrospinal fluid, and tissue from the donor and recipients for evidence of EEEV infection by multiple assays. We investigated blood transfusion as a possible source of organ donor infection by testing remaining components and serum specimens from blood donors. We reviewed data from the pre-transplant organ donor evaluation and local EEEV surveillance.

RESULTS: We found laboratory evidence of recent EEEV infection in all organ recipients and the common donor. Serum collected from the organ donor upon hospital admission tested negative, but subsequent samples obtained prior to organ recovery were positive for EEEV RNA. There was no evidence of EEEV infection among donors of the eight blood products transfused into the organ donor or in products derived from these donations. Veterinary and mosquito surveillance showed recent EEEV activity in counties nearby the organ donor's county of residence. Neuroinvasive EEEV infection directly contributed to the death of one organ recipient and likely contributed to death in another.

CONCLUSIONS: Our investigation demonstrated EEEV transmission through solid organ transplantation. Mosquito-borne transmission of EEEV to the organ donor was the likely source of infection. Clinicians should be aware of EEEV as a cause of transplant-associated encephalitis [2].

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Delekta PC, Dobry CJ, Sindac JA, Barraza SJ, Blakely PK, Xiang J, Kirchhoff PD, Keep RF, Irani DN, Larsen SD, Miller DJ. Novel indole-2-carboxamide compounds are potent broad-spectrum antivirals active against western equine encephalitis virus in vivo. J Virol. 2014 Oct;88(19):11199-214. doi: 10.1128/JVI.01671-14. Epub 2014 Jul 16. PubMed PMID: 25031353; PubMed Central PMCID: PMC4178776.
2)
Pouch SM, Katugaha SB, Shieh WJ, Annambhotla P, Walker WL, Basavaraju SV, Jones J, Huynh T, Reagan-Steiner S, Bhatnagar J, Grimm K, Stramer SL, Gabel J, Lyon GM, Mehta AK, Kandiah P, Neujahr DC, Javidfar J, Subramanian RM, Parekh SM, Shah P, Cooper L, Psotka MA, Radcliffe R, Williams C, Zaki SR, Staples JE, Fischer M, Panella AJ, Lanciotti RS, Laven JJ, Kosoy O, Rabe IB, Gould CV; Eastern Equine Encephalitis Virus Transplant Transmission Investigation Team. Transmission of Eastern Equine Encephalitis Virus from an Organ Donor to Three Transplant Recipients. Clin Infect Dis. 2018 Oct 29. doi: 10.1093/cid/ciy923. [Epub ahead of print] PubMed PMID: 30371754.