serotonin neurons in the dorsal raphe, dopamine neurons in the ventral tegmental area, and norepinephrine neurons in the locus coeruleus) contain subpopulations that also secrete an ionotropic transmitter (such as glutamate or GABA) (*10*), and the co-release of these neurotransmitters plays important roles in normal and disease conditions (*11*). However, understanding the mechanisms by which neurons can switch neurotransmitter phenotypes has remained challenging, and the present findings are an important advance in elucidating these processes.

The study of Li *et al.* is also important because it identifies an area of the brain that has not been previously implicated in fear generalization—namely, the serotonergic neurons in the lateral wing of the dorsal raphe. These neurons project to the lateral hypothalamus and the central amygdala, two regions involved, respectively, in innate fear and learned fear. Notably, the hippocampus, which is important for contextual discrimination, also projects to these two regions (*12*). It is therefore conceivable that the transmitter switch in the dorsal raphe allows for a bypass of the contextual discrimination that the hippocampus normally exerts on the lateral hypothalamus and the central amygdala, ultimately resulting in a generalized fear response. It will be important that future studies characterize the changes elicited in the lateral hypothalamus and the central amygdala by the transmitter switch and investigate how these changes affect downstream regions involved in fear, such as the periaqueductal gray that controls the freezing response. Because these regions also receive inputs from other neuromodulatory neurons [such as dopamine and nondopamine neurons from the ventral tegmental area that co-release GABA or glutamate (*13*)], it will be interesting to investigate whether those neurons also undergo transmitter switching, to define under which conditions this may occur, and to understand how common this phenomenon is. Finally, future studies should explore whether neurotransmitter switching is reversible and can be harnessed to modulate or even eliminate generalized fear, including in PTSD patients. ■

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GRAPHIC: N. CARY/*SCIENCE*

MEDICINE

An oral antiviral for Ebola disease

For those exposed to filovirus, such as Sudan virus and Ebola virus, a new study offers hope

By **Armand Sprecher** *and* **Michel Van Herp**

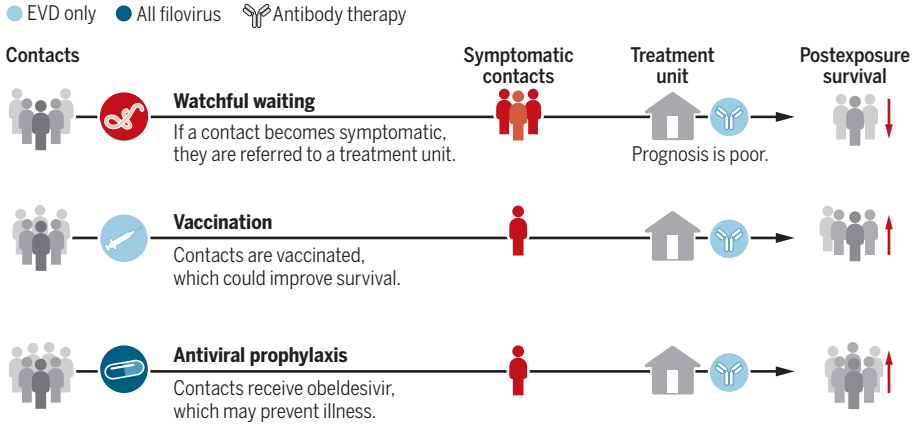
Marburg disease and Ebola disease—which includes Ebola virus disease (EVD) and Sudan virus disease (SVD)—are collectively called filovirus diseases (FVDs). These cause considerable mortality. During outbreaks, when a case of FVD is identified, their close contacts receive a daily visit from follow-up teams for 21 days, which is the extent of the incubation period. If a contact becomes ill, they are brought to a treatment unit, where they remain if they have FVD. This procedure should minimize spreading of FVD, but a substantial flaw is that people who have been exposed to someone with FVD are scared about the gravity of the disease and the limits of what can be done for them, and so they do not always volunteer for surveillance and isolation. On page 1195 of this issue, Cross *et al.* (*1*) report the efficacy of the oral antiviral drug obeldesivir in protecting cynomolgus macaques after SVD challenge, which could change attitudes toward surveillance.

The case fatality ratios (CFRs) for FVD outbreaks vary widely, depending on virus and context, but are usually around 60% (*2*, *3*). Before the West Africa EVD outbreak of 2014–2016, the largest outbreak of FVD was the SVD outbreak in Uganda in 2000, with 425 cases, of which 224 were fatal. The FVDs are all clinically similar: a febrile illness, often with muscle and joint pain, vomiting and diarrhea, and occasional bleeding from the nose, gums, or injection sites. Many patients will go into shock, develop multiorgan failure, and die (*4*).

The treatment unit where FVD patients and their contacts are treated and monitored is a place from which a lot of patients do not return, and thus many people do not want to go there. Being hospitalized in treatment units also means being isolated from one's family and loved ones while severely ill, and perhaps dying alone. Thus, visits from contact follow-up teams are an unwelcome daily reminder of potential illness and isolation; they also inform neighbors that a person may become a threat to the community. Many people endure contact-team visits and go to the treat-

Controlling filovirus disease outbreaks

When a person is diagnosed with a filovirus disease, such as Ebola virus disease (EVD) or Sudan virus disease, their close contacts are monitored. The current practice of watchful waiting results in referral to a treatment unit if the person becomes symptomatic, but prognosis is poor. However, vaccination and oral antivirals could serve as postexposure prophylaxis to reduce illness and increase survival. This might also increase the likelihood that close contacts will accept surveillance by follow-up teams.



ment unit if asked—some for the care that is offered, some to protect their families, and some because of social pressure. But many will flee or hide, and if they become ill, they will shed virus somewhere that is not under surveillance, possibly infect those around them, and perpetuate the outbreak.

Perhaps outbreaks would be easier to control if contacts could be offered something other than watchful waiting. Patients treated with the monoclonal antibody (mAb) therapies approved by the US Food and Drug Administration (FDA) for EVD had a CFR of ~35%, whereas the overall CFR was 66% during the 2018–2020 outbreak in the Democratic Republic of the Congo, where these therapies were studied (*5*). During EVD outbreaks, therapeutic mAbs could be used as postexposure prophylaxis (PEP) for contacts. Unfortunately, these therapies are expensive to manufacture and available only in limited quantities, and so they are presently reserved for the treatment of patients with confirmed disease or, rarely, as PEP for very high-risk exposures—for example, health care workers exposed to ebolavirus during patient care. The rVSV-EBOV vaccine appears to have some efficacy as PEP, at least in attenuating disease. A recent study showed that rVSV-EBOV reduced the likelihood of death in EVD patients by 44% when given two or fewer days before illness onset (*6*). Although achieving attenuated disease is promising, uptake of unfamiliar vaccines can be limited (*7*).

Obeldesivir is an oral prodrug that shares the same active metabolite as remdesivir—a broad-spectrum antiviral with preclinical efficacy against filoviruses that is also used to treat COVID-19 patients—and so it should have similar antiviral activity. Obeldesivir is now being studied for efficacy in treating COVID-19 (clinical trial NCT05715528). Cross *et al.* demonstrate that, like remdesivir, obeldesivir has in vitro efficacy against species of both *Ebolavirus* and *Marburgvirus*. It also fully protected cynomolgus macaques against a 100% lethal challenge with Sudan virus when a 10-day course was started 24 hours after challenge. Although other therapeutics, such as mAb treatments and remdesivir, are similarly protective against filovirus challenge (*8*, *9*), they are delivered intravenously, and this difference is where the potential value of obeldesivir lies.

The simplified administration of obeldesivir as an oral medication could increase the uptake of contact-tracing strategies. Additionally, as a small-molecule drug, it should be much less expensive to produce and be available in greater quantities than mAb therapies. These features could allow for the systematic delivery of PEP to all persons exposed to filovirus (see the figure). However, efficacy in nonhuman primate studies does not guarantee efficacy in exposed humans, so clinical trials will need to be carried out during future outbreaks. If the results of Cross *et al.* hold true for use in humans and can be replicated for other filoviruses, obeldesivir may be a solution to improving contact-tracing efforts and outbreak control. By offering preventive treatment to contacts, daily visits can be a more positive experience that is centered around their well-being, monitoring the effectiveness of PEP, and—for now, only in EVD outbreaks—a readiness to escalate to mAb treatment if needed. It is too soon to know whether obeldesivir PEP will change the relationship between the contacts and the follow-up teams, but it provides hope.

There are other reasons to be hopeful about the potential of obeldesivir. It could be a treatment for FVD survivors to eliminate virus from immune-privileged sites and thereby reduce the likelihood of sexual transmission, given that there is reason to believe that remdesivir does this (*10*). However, the advent of an effective vaccine and treatments for EVD has not brought about the change in outbreak control that was expected, at least not yet. Perhaps the benefit that obeldesivir may provide will not be entirely evident to the communities experiencing the outbreaks, and thus things may not change as much as hoped. Still, by addressing the needs of the people with whom follow-up teams must stay in contact and by offering them some hope, perhaps obeldesivir will prove to be what was needed to improve outbreak control. ■

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MATERIALS SCIENCE

Accelerating 2D materials discovery

A large-scale theory-driven approach predicts many new 2D materials

By **Anupma Thakur**[1] *and* **Babak Anasori**[1,2]

Two-dimensional (2D) materials are a class of nanomaterials that are sheets of one or a few atoms thick. They can be used in electronics, optics, energy storage, sensing, catalysis, biomedical, and environmental applications (*1*–*4*). Many 2D materials are made by slicing (exfoliating) bulk-layered structures to their thinnest layer of only a few atoms in thickness (*1*, *2*). However, without a full understanding of the interactions between the layers of atoms, simple trial-and-error experiments lead to slow progress in 2D materials discovery and substantial waste of resources from failed attempts. To circumvent these issues, a shift toward theory-driven experimental synthesis is essential. On page 1210 of this issue, Björk *et al.* (*5*) report high-throughput computational strategies with chemical exfoliation for synthesizing 2D materials. They used models to predict and guide the exfoliation process, which enhances efficiency and expands the family of 2D materials.

2D materials have intriguing properties, including high surface area, charge mobility, tunable bandgap, optical transparency, mechanical strength, and flexibility (*1*–*4*). Exfoliation leads to the confinement of charge carriers, heat, and phonon transport, resulting in distinct physical behavior in 2D materials (*1*, *3*). Additionally, the intrinsic properties of 2D materials can be modulated by the addition or removal of a few atoms within the 2D sheets and stacking different 2D materials, facilitating the development of precisely engineered devices (*1*).

2D materials are synthesized either by adding atoms one by one to make an atomically thin 2D sheet (bottom-up methods) or by exfoliation of a bulk layered material

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