Zhou *et al*. measured the electronic compressibility in moiré rhombohedral trilayer graphene and found it largely unchanged compared with the untwisted material, with the exception of extra energy gaps in the band structure introduced by the twist. The similarity between the behaviour of the ferromagnetic and superconducting states in rhombohedral trilayer graphene and moiré graphene systems might hint at a close connection between the mechanisms underlying these states.

Further studies in rhombohedral graphene will be required to confirm and determine the origins of these phases. For example, measuring a type of particle scattering known as Andreev reflection[9] will provide further evidence that the spins are fully aligned in the quarter- and half-metallic phases even in the absence of a magnetic field. The simple lattice structure and reproducibility of rhombohedral trilayer graphene could help theoretical and experimental studies aimed at revealing the nature of the phases identified by Zhou and colleagues — and might offer insights into other moiré graphene systems.

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Drug discovery

A step towards dengue therapeutics

Scott B. Biering & Eva Harris

Finding a treatment for dengue, the most prevalent mosquito-borne viral disease in humans, has been difficult. A compound called JNJ-A07 displays promising activity against dengue virus in mouse models of infection. **See p.504**

Despite immense effort spent in pursuit of a therapeutic for dengue, no treatment is currently available. An effective drug against dengue virus (DENV) is urgently needed, because this mosquito-transmitted virus represents a tremendous public-health burden, with about 3.9 billion people at risk of infection (see go.nature.com/3fbf9xz) and an estimated 51 million cases of dengue annually worldwide[1]. Several challenges have precluded the development of such a therapeutic: it must be administered orally, must rapidly lower the amount of virus in the bloodstream to stem progression to severe dengue, and must be similarly potent against all four main types of DENV (dubbed serotypes DENV-1 to DENV-4), all while exhibiting an acceptable safety profile. Excitingly, on page 504, Kaptein *et al*.[2] describe a compound that targets the dengue virus protein NS4B and ticks all of these boxes.

The lead candidate compound identified by Kaptein and colleagues, JNJ-A07, emerged from a set of 2,000 related molecules that were generated by making chemical modifications to a compound already selected for its ability to inhibit DENV-2-mediated cell death[3]. The authors found that JNJ-A07 was highly effective against all tested genetic variants of the four serotypes, including 21 different virus strains isolated from infected individuals. The effects of JNJ-A07 were tested in various cell types, including mosquito cells and human dendritic cells — a type of immune cell thought to be a key target of DENV infection in humans. Notably, this compound was not effective against other viruses, including other closely related members of the *Flavivirus* genus, suggesting that it is highly specific for DENV.

Because DENV is an RNA virus that evolves rapidly to escape antiviral pressures such as drugs, the authors investigated the ability of DENV-2 to escape the antiviral activity of JNJ-A07 in cell culture. Mutant virus strains that could escape the antiviral effects of JNJ-A07 were not detected until about 15 weeks after infection, and complete resistance of DENV-2 emerged only after about 40 weeks of continuous exposure to the compound. Resistance was correlated with mutations in the virus's RNA that caused substitutions of three amino-acid residues in the NS4B protein, suggesting that this protein is the target of the compound. The length of time taken to develop resistance and the requirement for multiple mutations suggest that the virus would have to overcome a high barrier to become resistant to JNJ-A07.

Crucially, the resistance mutations that enabled DENV-2 to escape the antiviral activity of JNJ-A07 in human cells also rendered the virus unable to replicate in mosquito cells. This indicates that, even if it did develop resistance to JNJ-A07 in individuals treated for dengue, the mutant virus would be at a 'dead end', given that it relies on mosquitoes for transmission to its next human host. Such a possibility is intriguing, and requires follow-up investigations in animal models.

The NS4B protein spans the membrane of an organelle in the host cell called the endoplasmic reticulum, and is crucial for the replication of DENV[4]. The protein interacts directly with another viral protein, NS3, which catalyses reactions involving proteins and nucleic acids[4]. The authors found that JNJ-A07 blocks the formation of the NS3–NS4B complex (Fig. 1). This mechanistic detail is valuable, but further structural studies demonstrating the direct interaction between JNJ-A07 and NS4B would provide insights into how it inhibits viral replication and could inform the design of other NS4B inhibitors. Further work should evaluate the ability of JNJ-A07 to interfere with other known interactions of NS4B (including those with the viral proteins NS1, NS2B and NS4A), and with other functions of NS4B, such as its ability to form dimers and to modulate the host's immune response[4].

Dengue virus does not normally replicate easily in mice. Therefore, the authors investigated the effects of JNJ-A07 in DENV-infected mice that had been genetically engineered to lack a set of proteins involved in interferon signalling, which is involved in the immune response to viruses. Kaptein and colleagues infected these immunocompromised mice with lethal or sublethal amounts of DENV-2, and found that JNJ-A07 was highly effective as an antiviral drug. It rapidly decreased virus levels in the bloodstream, reduced the production of inflammatory molecular signals called cytokines (which are thought to contribute to severe dengue disease) and prevented mice from dying of the infection. Furthermore, the efficacy of JNJ-A07 was observed when it was given either therapeutically (four to five days after DENV infection) or preventively.

The efficacy of this compound in mouse models warrants moving JNJ-A07 forward into investigations of its safety profile, how it moves around the body, its potency against all four serotypes in animals, studies in non-human primates and, eventually, if warranted, clinical trials in humans. It will also be crucial to assess the efficacy of JNJ-A07 in

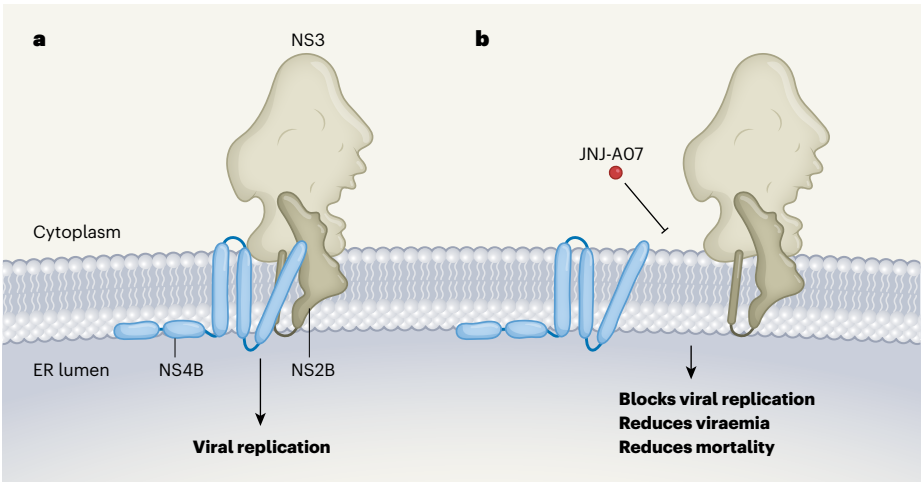

Figure 1 | A molecule called JNJ-A07 inhibits the replication of dengue virus. It has been challenging to find therapeutics for dengue disease. **a**, Replication of dengue virus, the agent that causes the disease, requires the formation of a complex that includes the viral proteins NS4B, NS3, NS5, NS2A, NS2B, NS4A and NS1 in the membrane encapsulating an organelle called the endoplasmic reticulum (ER) in host cells (NS4B, NS2B and NS3 are shown here). **b**, Kaptein *et al.*[2] identify a molecule called JNJ-A07 that can be delivered orally and reduces the levels of dengue virus in the blood of infected mice, when used preventively or therapeutically (after infection). The authors propose that JNJ-A07 blocks the binding of NS4B to NS3, preventing the formation of the viral replication complex and thus inhibiting viral replication, reducing both the amount of virus in the blood (viraemia) and mortality.

animals infected with DENV that have intact interferon signalling.

A property shown by the four DENV serotypes is that the presence of virus in the blood (known as viraemia) in an initial DENV infection usually results in a robust antibody response that provides protection against future infection and disease by the same serotype, as well as in the production of antibodies that cross-react with other DENV serotypes. If an individual's immune system produces a low-to-intermediate level of certain cross-reactive antibodies, there is an increased risk of more-severe disease after a subsequent infection with a different DENV serotype, through a phenomenon called antibody-dependent enhancement[5]. Therefore, when an infection is suppressed by an antiviral that lowers viraemia, does this alter antibody production in such a way that an individual is predisposed to antibody-dependent enhancement in a subsequent infection? This question must be considered when developing a dengue therapeutic.

Although JNJ-A07 displays excellent efficacy in the authors' mouse model, it is worth investigating whether combining this compound with other promising dengue therapeutics would yield synergistic antiviral activity against infection[6]. Candidates for possible therapeutics to combine include – but are not limited to – inhibitors of an enzyme called viral RNA-dependent RNA polymerase[7] (which catalyses the replication of the virus's RNA), or even other NS4B inhibitors, such as the compound NITD-688, which was shown to be highly effective in mouse models and targets NS4B through a potentially different mechanism from that of JNJ-A07 (ref. 8).

In summary, the authors have discovered an orally administered DENV-specific NS4B inhibitor that is effective against all four DENV serotypes, with a high barrier to resistance, a previously undescribed mechanism of action, and efficacy against one DENV serotype when administered preventively or therapeutically in mice. Although JNJ-A07 is not the first dengue NS4B inhibitor to be discovered[8–11], it is one of the most promising and well characterized. As such, the next challenge is to design clinical trials for JNJ-A07 in humans, paying particular attention to its use (preventive or therapeutic), the clinical outcomes (in treating non-severe or severe disease) and the target population (individuals who live in areas where dengue is endemic, or people visiting or travelling through such areas)[12].

Beyond this, ensuring that people with dengue seek treatment early in the viraemic phase of infection is a challenge that all dengue antiviral programmes will need to address. However, people could be more incentivized to seek treatment if they knew that a therapeutic finally existed. Although such challenges will be complicated to address, the fact that they can now even be considered represents a major advance in the field of dengue therapeutics.

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Applied physics

Non-magnetic objects moved by electromagnets

Eric Diller

A set of electromagnets has been used to move metal objects without touching them, even though the objects are not magnetic. This method could potentially be used like a 'tractor beam' to move hazardous objects in space. **See p.439**

Imagine trying to catch a fragment of a rocket nozzle in orbit above Earth's atmosphere. The fragment is travelling faster than a bullet, and tumbling rapidly end over end. Around 27,000 orbiting pieces of such debris are large enough to be tracked by the US Space Surveillance Network, and they constantly threaten active spacecraft and satellites. If the debris were magnetic, then magnets could be used to safely grab hold of the objects and dispose of them – but orbital debris tends to contain little or no magnetic material. On page 439, Pham *et al.*[1] report a method that allows magnets to grab non-magnetic objects from a distance,