of antigen-presenting cells (APCs), the immune cells that recognize antigens and trigger immune responses. When the PPAS encounters the cell membrane of an APC, the oil droplets flatten, resulting in increased surface contact at the droplet–cell interface (Fig. 1). The mobile antigens on the droplet surface then migrate to the cell interface, increasing the local antigen density and triggering phagocytosis of the droplet and antigen delivery to the cell. The authors show that the PPAS is superior to PLGA nanoparticles, PLGA microparticles and traditional surfactant-stabilized emulsions because of its ability to enhance antigen uptake and presentation by antigen-presenting dendritic cells, which have a critical role in the induction of antigen-specific immune responses after vaccination.

An exciting ability of the PPAS is its ability to enhance the induction of antigen-specific $CD8^+$ T cells after immunization with a protein antigen. Antigen-specific $CD8^+$ T cells play an important role in killing tumour cells or virus-infected cells, and traditional adjuvants widely used in humans, such as alum, typically do not induce antigen-specific $CD8^+$ T cells[2]. The authors hypothesize that nanoparticle charge reversal takes place after APC phagocytosis, resulting in antigen leakage into the cytosol of the cell, and that its subsequent cross-presentation drives a $CD8^+$ T cell response. Indeed, immunization with protein antigens formulated with the PPAS more than doubled the number of antigen-specific $CD8^+$ T cells and showed enhanced survival against a lethal viral infection or tumour challenge when compared with another emulsion or PLGA particle adjuvant formulation. More importantly, the PPAS was superior to adjuvants currently approved for human use (such as alum or MF59) for the induction of protective immunity against a tumour challenge. Additionally, the PPAS was superior to alum and comparable to AS04 for the induction of protective immunity against a lethal influenza virus challenge.

Collectively, Ma and colleagues have made a significant contribution to the vaccinologist's toolbox by providing a unique adjuvant system, and their findings could also lead to advances in other drug delivery systems. However, additional studies are needed to improve the stability of the PPAS, and fully determine its safety, efficacy, general applicability and use in a clinical setting. Studies with many other different antigens are required to establish the stability and versatility of the system. The authors comment that the antigen-loading efficiency of the PPAS was reduced with larger molecular weight or small peptides, and that "it might be tuned by altering the size of the assembled nanoparticles", although a systematic investigation of these issues was not performed. Vaccine formulations must be safe and injection site reactions have been observed with other potent adjuvants[9]. While the authors demonstrated the safety of the PPAS by monitoring serum biochemical parameters in mice that had received three doses of the PPAS, injection site reactions based on histological evaluation of the injection site will be needed to ensure that the adjuvant system is fully safe. Moreover, immune responses observed in mice often do not translate to non-rodent species or humans. Thus, studies with the PPAS in other preclinical models such as rabbits, pigs (their skin is similar to humans) and non-human primates are needed to better understand the safety and efficacy of this adjuvant system. Despite these shortcomings, the PPAS developed by Ma and co-workers is a promising alternative to conventional adjuvant approaches and may have wider implications across human medicine. Beside its use as an enhancer of protection against tumour and viral challenges, the PPAS may be useful for immunotherapy targeting allergic diseases[10]. Finally, it may also be explored as an immune modulator by combining this formulation with distinct ligands recognized by receptors that tune immune cell responses such as Toll-like receptors[2,4,5] and elicit specific immune responses in the very young or very old[11]. ❐

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Competing financial interests

D.J.B. is co-founder and chief operating officer of a company identifying and developing immunomodulators.

ANTIMICROBIALS

Broad-spectrum antivirals

Nanoparticle mimics of heparan sulfate proteoglycans offer a new strategy for the inhibition of a range of viral infections.

Benson J. Edagwa and Howard E. Gendelman

Viral infections commonly lead to significant morbidity and mortality. A third of deaths from all infectious diseases worldwide are of viral origins[1]. While the most effective means to combat such infections are vaccinations[2], treatment and prevention measures can often be achieved with medicines. However, a number of therapeutic challenges hamper the development of effective antiviral therapy such as the limited spectrum of most antivirals and inherent drug toxicities. A notable step forward is reported in the current issue of *Nature Materials*. Francesco Stellacci and colleagues[3] describe broad-spectrum antivirals employing nanoparticle-formulated mimics of heparan sulfate proteoglycans (HSPG).

Antiviral medicines have been designed to block specific stages of the viral life cycle by viral receptor binding, penetration,

uncoating, nucleic acid chain elongation, transcription, translation and assembly, and release[4] (Fig. 1a). Any or all attempts to use such regimens to eliminate viral infections have encountered drawbacks due to common viral mutations and virus heterogeneity. These lead to microbial sequestration and consequent escape from immune surveillance[4] independent of latent infections. Limitations in delivery and maintenance of inhibitory antiviral drug concentrations at viral growth sites have also slowed pharmacologic success[4,5]. Such restricted activities in antiviral drugs have highlighted recent research activities for human immunodeficiency virus (HIV) and Ebola virus prophylaxis, treatment and vaccine preventative measures. Improving the balance between the antiviral and host cell homeostasis underlies any drug therapeutic index[6]. The search for nontoxic and broadly active agents that inhibit a range of viral infections remains urgent. While interferons and ribavirin are used to fill this niche, both commonly cause flu-like symptoms, chest pain and diarrhoea while demonstrating limited antiviral activities[4,6].

A means of improving antiviral agents is to repurpose already approved drugs[7]. Nanomaterials have been widely utilized for drug delivery in a number of applications. They can also be employed in the delivery of antiviral agents to sites of viral replication by using cells as depots. Macrophage carriages as vehicles for drug dissemination in viral reservoirs can be achieved using this approach. Antiviral nanoparticles 'hide' within endosomal depots that enable long-term cell-based drug storage. Stability is realized and ensured through the cell's own Rab GTPases serving to coordinate particle drug trafficking, vesicle formation, movement, fusion and release (Fig. 1b). Drug particles that are retained in Rab endosomal depots are delivered to tissues infected with viruses by mobile cells[7]. This nanoparticle-based strategy may also be deployed to target a spectrum of intracellular pathogens, such as *Mycobacterium tuberculosis*. It may also be employed in antiviral gene therapies utilizing CRISPR/Cas9 and broadly neutralizing antibodies being developed to eliminate viral infections[8,9]. Nonetheless and even considering such advances, the narrow spectrum and target specificity of such agents pose risks for viral drug resistance.

As a suitable alternative to overcome such antiviral therapeutic challenges, Stellacci and colleagues developed unique nanoparticles coated with mercapto-1-undecanesulfonate-containing ligands of long and flexible linkers that mimic HSPGs and permit strong association

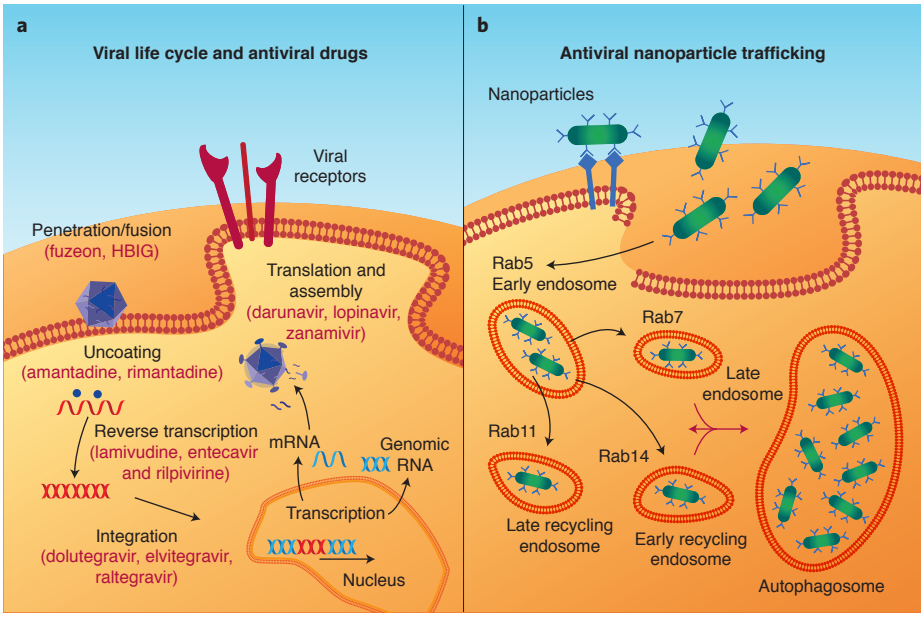

Figure 1 | Virus lifecycle and intracellular delivery of antiviral agents. **a**, The stages in the life cycle of viruses have provided targets for drug development and action. Attachment of a virus to cell receptors can be prevented by antiviral agents such as fuzeon (for HIV) or by antibodies to hepatitis B (HBIG) that inhibit fusion of viral and cellular membranes. Antiviral agents that act by interfering with viral uncoating and replication include amantadine and rimantadine. These agents inhibit proton transport in the M2 ion channel of influenza. Other drugs are designed to modify nucleic acid synthesis, viral integration, transcription, translation and assembly. These include nucleoside and non-nucleoside reverse transcriptase inhibitors such as lamivudine, entecavir and rilpivirine (HIV and hepatitis B virus). The anti-HIV integrase strand transfer inhibitors affect viral genome insertion into the DNA of the host cell. Examples include dolutegravir, elvitegravir and raltegravir. Antiviral agents that inhibit viral translation and assembly include zanamivir (influenza), and darunavir and lopinavir (HIV). **b**, Intracellular delivery of antiviral nanoparticles can improve drug carriage across cellular membranes and facilitate depots in subcellular endosomes (Rab endosomes) at sites of active viral replication.

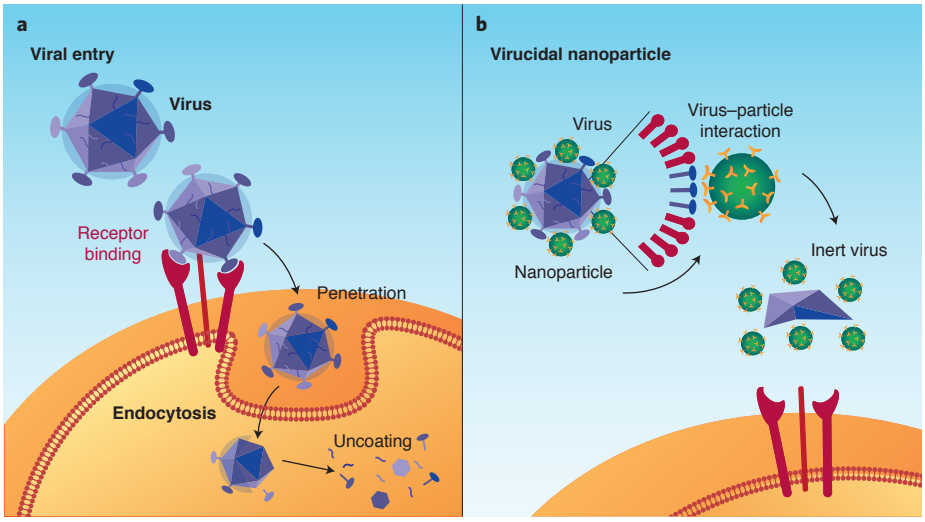

Figure 2 | The mechanism of action of virucidal nanoparticles. **a**, The attachment and entry of a virus into the host cell is facilitated by specific host cell receptors. **b**, The receptors can be blocked by virucidal nanoparticles (green spheres) modified with sulfonated HSPG (orange spikes) that bind irreversibly to viral glycoproteins. This will subsequently alter the viral configuration and block receptor-mediated entry into the cell, resulting in an inert virus, thus neutralizing infection. Such 'decoy' nanoparticles are described by Stellacci and colleagues in preventing viral infections.

with viruses[3]. These new agents target the earliest events of virus–cell interactions (Fig. 2a). Virucidal sulfonated nanoparticles with longer lipophilic spacer arms, based on HSPG structure and function, facilitate viral attachment to the particle. The authors document strong multivalent and irreversible interactions between the virus and nanoparticles. Remarkably, binding of a virus by these antiviral nanoparticles leads to irreversible virus deformation, thus destroying the ability to elicit new infections (Fig. 2b). Efficacy and mechanistic binding studies on viral protein–nanoparticle interactions also revealed that fusion of nanoparticles with the virus exerted pressure on the virus membrane that caused disintegration of viral capsids. This so-called 'microbial vacuum cleaner' was effective in neutralizing a broad spectrum of viruses including herpes simplex, human papilloma, dengue and respiratory syncytial viruses, with the likelihood that more will be susceptible to the platform. In contrast to other nanotherapeutics, this new platform uses a novel antiviral mechanism that blocks virus binding to its HSPG 'receptors'.

The approach developed by the authors shows real potential for development of safe and effective antiviral therapy[10]. However, several challenges are noteworthy. Future studies are required to demonstrate whether these virucidal nanomaterials are safe in the longer term. Cross-validating efficacy studies require that the novel nanoparticles retain viral potency. Moreover, investigations are required on whether the agents maintain target specificity during emergence of viral mutations. On balance, the work by Stellacci and colleagues offers clear proof of concept and key insights for a novel approach to broad-spectrum antivirals with the potential of improving safety and efficacy for future clinical translation. New pathways leading to the development of broad-spectrum antivirals would combat the remaining major health crisis and someday affect a functional viral cure. ❐

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MINIATURE LASERS

Is metal a friend or foe?

A thorough study comparing the performance of more than a hundred photonic and plasmonic lasers concludes that the latter are advantageous when their cavity volumes are close to the diffraction limit.

Mikhail A. Noginov and Jacob B. Khurgin

A long-standing question debated among the nanophotonics community is whether size matters and helps to reduce the threshold of micrometre- and submicrometre-sized lasers, and whether the presence of metal interfacing the gain medium harms or improves the laser performance. In a work published in *Nature Communications,* Ren-Min Ma and colleagues[1] address this issue through a thorough experimental study, and conclude that when the device dimensions approach the diffraction limit, plasmonic (metal-based) lasers have superior performance over traditional photonic lasers as they are faster and have lower threshold and lower power consumption (Fig. 1).

A laser has two major components: (i) a gain medium providing for stimulated emission and light amplification, and (ii) a resonator facilitating stimulated emission feedback (loosely speaking, reflecting generated photons to the place of their origin and, in many cases, enabling a coherence of laser radiation). The most basic laser cavity supporting standing-wave oscillation modes consists of two parallel mirrors, the distance between which is equal to an integer number of 'half-wavelengths' ($\lambda/2$) of laser radiation. Therefore, the minimum distance between the mirrors is equal to $\lambda/2$, which is equivalent to ~250 nm in the visible part of the spectrum — an order of magnitude larger than the typical size of a modern transistor. This hinders the dream of keeping up with the Moore's law by replacing electronic circuits with much faster optical circuits[2], which would require laser-based sources and amplifiers of coherent light.

A novel solution to the size problem was put forward in 2003 by Bergman and Stockman[3], who proposed to change the feedback mechanism and replace a set of large (by the nanoworld standards) mirrors with a nanoscopic metallic structures that support resonant oscillations of free electrons (weakly) coupled to modes of electromagnetic radiation — the phenomenon known as a localized surface plasmon. The proposed device, termed spaser, which can be as small as a few nanometres, was primarily intended to generate surface plasmons (rather than photons) and be directly integrated into optical frequency circuits[4]. The first experimental demonstration, in 2009, of the spaser-based nanolaser[5], in which the 14-nm Au plasmonic nanoparticle, providing for a stimulated emission feedback, was surrounded by the 44-nm dye-doped silica shell, providing for gain, was followed by a rapid development of a variety of micrometre- and submicrometre-sized plasmonic lasers (or spasers)[6], bringing the dream of nanocircuitry operating at optical frequency closer to reality.

Besides the very possibility of having a laser whose size is not limited by $\lambda/2$ — which, not coincidentally, is close to the diffraction limit for light (the minimum area into which the light can be focused) — the heuristic expectation that