stars and an older, chemically evolved population, respectively emitting most of the UV and optical light. Sobral *et al.* corroborated these model-based predictions using images obtained by the Hubble Space Telescope which show that CR7 consists of three spatially separated clumps.

This structure is consistent with a theoretical study[10] that proposed the 'inside-out' formation of population III stars. The authors' observations suggest that a wave of star formation swept over CR7, progressively moving outwards from the old red clumps towards the young, UV-bright clump 5 kiloparsecs away, where population III stars are inferred to exist. This distance is large enough to prevent contamination of the UV-bright clump by metals created in the structure's interior. According to this picture, photons from the old stars not only helped to ionize a large bubble around them, but also prevented any surrounding gas from forming stars for some time by impeding the gas's gravitational collapse. This created an ideal environment for population III stars to eventually form in the chemically pristine clump, while allowing the Lyman-α photons to escape because there was no neutral hydrogen to absorb them. This formation mechanism implies that, in Lyman-α emitters, population III stars would most probably be detected in hybrid stellar populations.

Sobral and colleagues' discovery of this population III system is not without caveats. For example, to match the ratio of helium-to-Lyman-α line emission predicted by models, the authors deduce that 75% of the Lyman-α emission must have been lost through scattering or absorption. In addition, the proposed scenario in which evolved, 'second-generation' stars can ionize a region without chemically polluting it, while also conveniently holding back star formation in the vicinity until population III stars arise, seems somewhat ad hoc, although it is not impossible. Finally, the authors state that the properties of CR7 can also be explained by gas falling into a black hole formed from the direct collapse of primordial gas, another theoretical construct. However, material around black holes produces broad emission-line profiles and X-ray radiation, neither of which are detected in the current observations. Deep observations with next-generation X-ray telescopes might be able to distinguish between the population III and black-hole scenarios[11].

Overall, Sobral *et al.* present the most promising observational evidence for the existence of population III stars found so far. An immediate implication of the CR7 finding is that these stars may be more readily detectable than previously thought. Rather than existing solely in isolation in the earliest galaxies, metal-free stars may also form alongside evolved stellar populations. Therefore, all luminous Lyman-α emitters are excellent candidates for harbouring population III stars and, as such, are ideal targets for the James Webb Space Telescope, the next-generation infrared observatory. This telescope's unprecedented sensitivity will enable it to detect both bright and faint metal emission lines in the optical spectra of distant galaxies, and to confirm whether CR7 and similar systems contain the elusive population III stars. ■

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NANOTECHNOLOGY

# Platelet mimicry

**Cloaking drug–loaded nanoparticles with platelet membranes enhances the drugs' abilities to target desired cells and tissues. This technology might improve treatments for cardiovascular and infectious diseases.** SEE LETTER P.118

OMID C. FAROKHZAD

The development of nanoparticles that can carry drugs to target sites in the body promises safer and more-effective drug delivery to solve myriad medical problems. It has proved difficult to create the complex exterior surface that allows these nanocarriers to undergo 'normal' biological interactions[1,2], but, by turning to nature for design cues, scientists have begun to develop such biomimetic nanoparticles[3,4]. On page 118 of this issue, Hu *et al.*[5] report that nanoparticles coated with the membrane of blood platelets are shielded from the body's immune responses, and possess platelet-like binding properties that allow them to target desired cells and tissues. Alongside broad therapeutic implications, the study blurs the line between materials science and biochemistry, introducing techniques that could benefit both nanoengineering and biomembrane research.

When blood vessels are damaged, the injury exposes proteins such as collagen that are abundant in the subendothelial layer underneath the vessel lining. Platelets — small, non-nucleated membrane-bound cell fragments circulating in the blood — bind to these proteins with strong affinity and then release blood-clotting factors, promoting the formation of a platelet plug that helps to heal the wound. Because many conditions, including cancer, inflammation and trauma, are associated with vascular

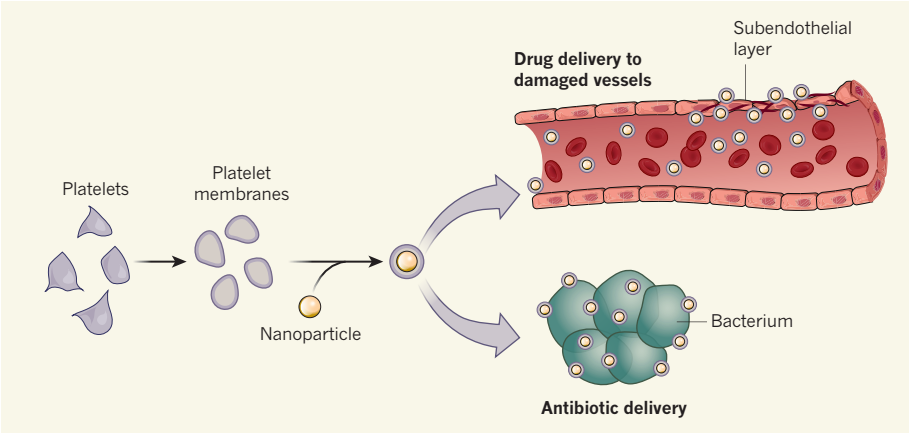


**Figure 1 | Designing nanocarriers.** Hu *et al.*[5] have developed nanocarriers that improve drug delivery to desired targets. The authors isolated the membranes of platelets from human blood and used them to cloak synthetic nanoparticles loaded with drug. These nanocarriers mimic the biological properties of platelets, enabling them to evade immune detection in the body. They can bind to the exposed subendothelial layer of damaged vessels, improving drug delivery for many diseases associated with damaged vasculature, and can also improve antibiotic delivery to bacteria in the body. (Adapted from ref. 5.)

damage, platelets have long inspired drug-delivery research. Nanoparticles have been engineered to display platelet-like ligands on their surface, which facilitates binding to subendothelial components[6,7]. In addition, platelet morphology and clotting mechanisms have been modelled, with the aim of enhancing drug targeting[7,8]. However, such efforts have failed to produce nanoparticles that can truly mimic the behaviour of platelets.

Platelets have also attracted interest in studies of infectious disease, because several bacterial species express surface proteins that interact with platelet receptors. This platelet–bacterium interaction has been linked to lethal complications during infection[9]. For instance, the high volume and velocity of blood that passes through the heart valves make that area susceptible to injury, and, in infective endocarditis, invasive microbes adhere to injured valve surfaces and promote further platelet aggregation. This is a serious therapeutic challenge, because the clot-encased microbes at the valve are inaccessible to antibiotic treatment and evade the immune response. Without effective intervention, approximately 40% of hospital patients who contract infective endocarditis will die[10].

The researchers behind the current study have previously developed nanoparticles coated with the membranes of red blood cells and cancer cells, and have shown that these nanoparticles can be used to neutralize bacterial toxins and for anti-cancer vaccinations, respectively[11–13]. Building on this success, Hu *et al.* developed polymeric nanoparticles coated in platelet membrane that mimic many of the biological functions of platelets (Fig. 1). Imbuing the nanoparticles with platelet-like properties was a notable challenge, but the authors took advantage of the fact that there is a differential charge distribution between the outer and inner surface of the platelet membrane, due to the abundance of negatively charged sialic acid molecules on the outer surface. Hu and colleagues made their nanoparticles negatively charged and so, through electrostatic-charge repulsion with the platelets' outer membranes, the nanoparticles preferentially bound to the inner membrane. This ensured that the membrane was 'right-side-out' on the nanoparticle surface.

Hu and co-workers' nanocarriers have a more complete set of membrane proteins than previous platelet-mimicking nanoformulations — the nanoparticles were coated in 15 immunomodulatory and subendothelial-binding components. This membrane cloak enabled the particles to bind effectively to human collagen in *in vitro* assays, and to target regions of damage in isolated blood vessels. The authors demonstrated that the nanocarriers successfully evaded detection by immune cells, and were well tolerated by rodents.

The narrowing of arteries or valves as a result of excessive cell proliferation can pose problems following corrective surgery. Hu and colleagues' nanoformulation effectively prevented vessel thickening in a rat model of this disorder, which is known as restenosis. The nanoparticles selectively bound to injured arteries, enabling the sustained release of an antiproliferative drug.

Perhaps more exciting is the nanoparticles' ability to target bacterial species that adhere to platelets. Targeted antibiotic delivery is a major research topic given the rising threat of antibiotic resistance. However, identifying an injectable and broadly applicable pathogen-targeting particle has been a technical hurdle to developing antibacterial nanocarriers. The authors showed that their technology could overcome this challenge for the bacterium *Staphylococcus aureus*, a common pathogen. Compared with free antibiotic, the nanoparticles improved delivery of antibiotics to the bacteria both *in vitro* and in infected mice. This ability to specifically target bacteria might enable platelet-membrane-coated nanoparticles to tackle severe complications of infection, such as the presence of bacteria in the blood, which can cause sepsis and the spread of infection. And by directing higher drug doses to the pathogen, these nanoparticles offer the hope of boosting the effectiveness of antibiotics whose efficacy is on the wane.

Given the innovative nature of Hu and colleagues' nanocarriers, manufacturing and regulatory standards must be established before they can be used in the clinic. The past decade has seen considerable advances[1] in establishing best practice in this area — there have been improvements in the processing of human blood products to enhance their preservation and function, and complex synthetic nanocarriers have been engineered and used in human clinical trials. Extra risks must be taken into account when designing nanocarriers that combine biological and synthetic components, but the biotechnology industry has the operating procedures in place to meet the required standards. These are exciting times in nanomedicine. The authors' biomimetic nanoparticles mark a new frontier, providing a glimpse into the future of the field. ■

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PHENOLOGY

# Spring greening in a warming world

**Warmer temperatures have been associated with an earlier emergence of spring leaves each year. New data, however, suggest that leaf emergence is becoming less sensitive to temperature as global temperatures rise.** SEE LETTER P.104

TREVOR F. KEENAN

For centuries, people have been fascinated by the timing of the arrival of spring, a season named for the 'springing forth' of the leaves of deciduous trees. It has long been known that spring leaf emergence is strongly linked to temperature[1,2] — even in ancient Rome, Pliny the Elder realized that leaf emergence was a much better indicator of weather than were the constellations[3]. Leaves have emerged earlier over the past century, as spring has become warmer. With global anthropogenic emissions currently exceeding previous worst-case scenarios[4], considerable warming is expected in the coming decades. Will future warming lead to even earlier and greener springs? In this issue, Fu *et al.*[5] (page 104) report results suggesting that the relationship between the seasonal timing of leaf emergence — spring phenology —and temperature is changing.

The relationship between spring temperatures and leaf emergence has allowed scientists