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

ELENA ELISSEEVA/ALAMY

Figure 1 | Green and early. Temperature is the dominant factor in inducing the onset of spring leaf emergence in temperate deciduous forests. But Fu *et al.*[5] suggest that factors such as reduced winter chilling are decreasing the sensitivity of spring leaf emergence to temperature.

of the Intergovernmental Panel on Climate Change to use changes in the timing of emergence as a key indicator of the ecological impact of climate change[6]. Apart from resulting in a greener spring, earlier leaf emergence affects various aspects of ecosystem function, and generates multiple feedbacks to the climate system[7]. It has thus been built into state-of-the-art Earth-system models, which predict a large advance in the timing of leaf emergence under future climate warming. To test the relationship between leaf emergence and warming, Fu and colleagues examined 33 years of observations of 7 forest species across 1,245 sites in Europe. Surprisingly, they discovered that spring leaf emergence has been getting less sensitive to temperature over time (Fig. 1). Their observation-based results call into question current model projections, and suggest that spring leaves might not emerge as early under future warming as had been previously expected.

Although it is generally accepted that temperature is the dominant driver of spring phenology in temperate deciduous forests, there is considerable uncertainty about the pathways of temperature's influence, with little agreement between models, experiments and observations[8,9]. The timing of warming matters[10], and the response seems to vary by species and perhaps by location or population[11]. Many other factors could also play a part — primarily day-length (photoperiod) and winter-dormancy requirements, but also humidity and temperature variance. Photoperiod has been shown to have a strong influence on some species, particularly on the *Fagus* (beech) genus, for which the effect of warm temperatures is limited if the days are too short[12].

Many species have also been shown to require a certain amount of chilling in winter before their release from dormancy[13]. This evolutionary mechanism, which is designed to prevent the costly damage a late frost can inflict on young leaves, ensures that winter has truly passed before leaves emerge. Changes in any of these factors could potentially modify the temperature response of leaf emergence, and explain the observed decline in temperature sensitivity reported by Fu and colleagues.

The authors tested three hypotheses to examine the potential underlying causes of their observations. They assessed the role of photoperiod, but could neither confirm nor rule out its influence. They also found no significant changes in the timing of leaf emergence due to temperature-variance changes, which suggests a limited role for this factor. The third hypothesis tested was that warmer winters had resulted in reductions in winter chilling, which could dampen the response of spring leaf emergence to a warmer spring. Using multiple models, the authors showed that declines in winter chilling could indeed lead to a lower temperature sensitivity, although the change in temperature sensitivity predicted by the models was considerably smaller than that observed.

This long-term trend of a decline in winter chilling, in concert with a decline in the temperature sensitivity of spring leaf emergence, raises questions about the extent to which factors such as chilling requirements are already limiting the response of spring phenology to climate warming. However, the association falls short of a causal attribution, as the authors note, because temperature sensitivity was not observed to be markedly different in years that had more chilling than in years with less chilling. Furthermore, not all deciduous plants have chilling requirements, and many have low requirements that are met even under experimental warming[14]. For most species, the effect of chilling requirements is poorly understood.

The declining temperature sensitivity reported by Fu and colleagues is intriguing, but its root cause is still uncertain. More research is needed to assess whether other species and locations demonstrate a similar decline in temperature sensitivity — in particular, to examine the many other long-term records around the world, in combination with satellite observations of vegetation, experimental data and theoretical understanding.

Leaves emerge in spring as a result of responses that are hard-wired into the genetic code of trees. This might suggest that the response of phenology to environmental drivers should be highly predictable[15], yet we are far from having a predictive science of phenology. Observations such as those presented by Fu *et al.*, which challenge models and contemporary understanding, go a long way towards getting us there. ■

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