libraries. As an example, they take a library of 11 billion molecules, prioritize approximately 2 million of these molecules for screening on the basis of their 3D structure and the structure of the target site, and still identify biologically active compounds. Notably, the authors achieved this without compromising the accuracy of docking — the computational estimation of the binding affinity of a compound to a target.

V-SYNTHES takes advantage of the modular nature of large virtual libraries of readily accessible compounds — molecules that can be synthesized relatively easily. The approach uses an iterative cycle of library preparation, enumeration (the creation of organized lists of molecules), docking and then selection, to search efficiently for hits (Fig. 1).

The authors began by building a small virtual library of only about 600,000 fragments — small compounds that have a low molecular weight — that together aim to represent all the different structural motifs, known as scaffolds, present in the entire virtual library. The authors then used docking to score how well each fragment could bind to the target. By docking only this relatively small number of scaffolds in this first round, Sadybekov and colleagues were able to take forward high-scoring scaffolds for improvement. To improve them, the authors added synthons (small segments of a molecule) to the promising scaffolds. This step generates a new library of more-complete compounds that are, in turn, docked and scored before the highest-scoring are selected — and the cycle continues. With each iteration, the size of each compound increases as the molecules become more complete.

Sadybekov *et al.* first demonstrated the power of V-SYNTHES on two target proteins: cannabinoid receptors 1 and 2. The authors found that about one-third of the top 60 compounds predicted by V-SYNTHES to bind to and inhibit the activity of these receptors at low compound concentrations indeed showed such effects *in vitro*. This 'hit rate' is about double that achieved by the standard methods used by the authors, and yet V-SYNTHES required 100 times less computational resources than do such methods. The authors then tested V-SYNTHES on a kinase enzyme called ROCK1 and report a 28.5% hit rate: 6 of the 21 most promising compounds selected for synthesis and testing *in vitro* could bind to and inhibit the ROCK1 enzyme at compound concentrations of less than 10 micromolar. Such compounds could be suitable leads for further optimization in a drug-discovery programme.

V-SYNTHES represents a combination of two major approaches for the initial stages of drug discovery: structure-based and fragment-based drug design. In structure-based design, the structural characteristics of molecules and their interactions with a target are used to inform the design process. In fragment-based drug design, molecular groups are added to fragments that are initially identified as promising because of their potential activity.

This paper paves the way for identifying biologically active molecules from the large compound libraries that are now available (see go.nature.com/3emc4zm), using a fraction of the computational resources and time required by standard virtual screening methods, and with increased success. Crucially, the computational cost of the method scales with the number of synthons used, rather than with the size of the initial, main library. Therefore, the method will continue to be computationally feasible as libraries of readily available chemicals and their combinations continue to grow.

The scaling of V-SYNTHES means that users will be able to search for and find biologically active molecules in exceptionally large virtual compound libraries. The method is not guaranteed to find the best hits, but this might not matter much, because suboptimal hits often provide good starting places for the drug-development process. The larger problem for virtual screening is that, however fast the method, its results depend on the accuracy of the docking step. As for all virtual screening methods, the ability of V-SYNTHES to identify good hits depends on the accuracy of the docking scores estimated for the scaffolds, ranging from small fragments to complete molecules, and a truly reliable docking score has yet to be developed[4,5].

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Chemical biology

Nanoparticle asymmetry shapes immune response

Alexander Hooftman & Luke A. J. O'Neill

The chirality, or handedness, of nanoparticles is shown to be a key factor in determining how well such particles engage with the immune system — a finding that might help to inform the design of vaccines and anticancer therapeutics. **See p.366**

Shape is all-important for molecules, especially when it comes to a property known as chirality (handedness). A chiral molecule exists in two forms, called enantiomers, that are chemically identical, but are mirror images of each other, and that interact with other molecules in different ways. Chiral molecules have long been used in drug design — and some molecules can even be tailored to interact with the body in enantiomer-specific ways. On page 366, Xu *et al.*[1] report that chirality can also be used to design nanoparticles that have identical chemical structures, but that differ in their ability to activate immune cells, owing to differences in the spatial arrangement of their atoms.

Nanoparticles can exhibit chirality on different scales — both at the level of the molecules interacting with a cell, and on the much larger scale of the particles themselves. Understanding which type of chirality is interacting with a cell requires a synthesis protocol that decouples their effects. Xu *et al.* achieved this by using circularly polarized light, in which the electromagnetic field of the light wave rotates in a plane perpendicular to the direction of its motion. Molecules or nanoparticles that absorb left- and right-handed circularly polarized light differently are chiral. Using this method to synthesize left- and right-handed enantiomers of gold nanoparticles allowed the authors to change the degree of asymmetry of the nanoparticles by tuning the parameters of the polarized light. This, in turn, meant that they could correlate chirality with the strength of the immune response.

The authors tested the efficacy of their nanoparticles by performing experiments on the immune cells of mice — both in culture and in living animals. Although they found that both nanoparticle enantiomers could elicit immune responses, the left-handed enantiomer had a stronger effect than the

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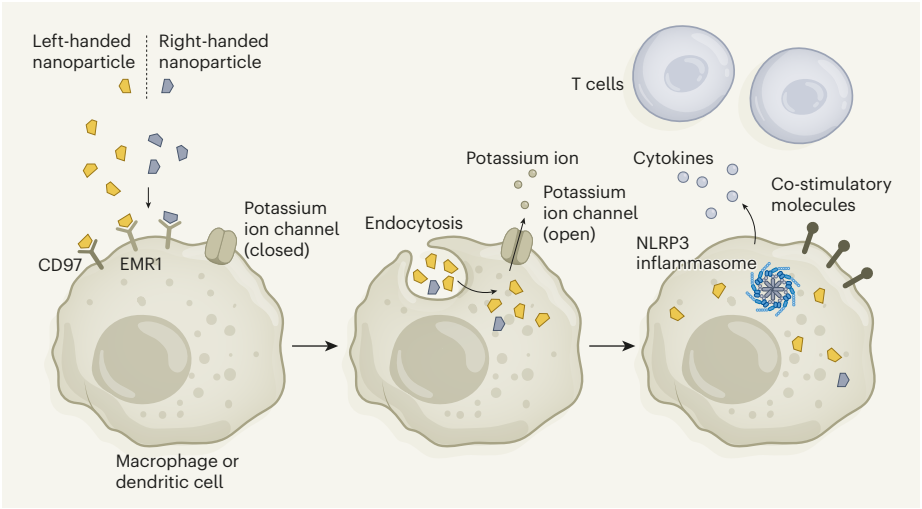

Figure 1 | Nanoparticles with different chirality can assist the immune system. Nanoparticles can activate macrophages and dendritic cells (two crucial cell types of the immune system) to increase the efficacy of a vaccine or defensive inflammation. Xu *et al.*[1] report that gold nanoparticles with left-handed chirality are more efficient at entering these cells than are their right-handed counterparts. Both types of nanoparticle engage with the receptors CD97 and EMR1 on the cell surface, but left-handed particles do so with higher affinity. The particles are then transported into the cell through a process known as endocytosis. Once inside the cell, they trigger the opening of potassium ion channels in the cell membrane. This, in turn, activates the NLRP3 inflammasome, a protein complex that senses foreign material. The nanoparticles induce the production of cytokines (proteins that mediate immune-cell growth and activity) and increase the expression of co-stimulatory molecules (which activate a response to foreign bodies), both of which are required to activate immune cells called T cells.

right-handed enantiomer. Several different types of measurement confirmed that the left-handed enantiomer was twice as efficient at entering immune cells as was the right-handed enantiomer. Further analysis confirmed that this difference was due to the nanoscale chirality of the particles.

Xu *et al.* also examined how the gold nanoparticles affected macrophages and dendritic cells, because these two types of immune cell are responsible for the early recognition of noxious substances or fragments of foreign proteins called antigens (Fig. 1). Dendritic cells are crucial for initiating immune responses that are specific to the antigen involved. This response can, in turn, lead to a long-lasting immune memory, as occurs after infection and also in response to vaccines.

The left-handed enantiomers of the gold nanoparticles induced macrophages *in vitro* to produce cytokines, which are proteins that mediate the growth and activity of immune cells. They also caused dendritic cells *in vitro* to increase their expression of molecules triggering co-stimulation — a signal that activates a response in an immune cell when it encounters an antigen-presenting cell. Both responses are required for the activation and recruitment of immune cells called T cells. When the authors injected live mice with the left-handed enantiomer, they obtained similar results.

They then generated nanoparticles that had varying degrees of chirality, as measured by a factor that describes the asymmetry between the absorption of left- and right-handed circularly polarized light. They found that there was a correlation between this asymmetry factor and the strength of the elicited immune response.

The nanoparticles were taken up by immune cells through a process called endocytosis, which involves the particles first adhering to specific receptors on the cell surface and then moving into structures known as lysosomes, from which they then burst out into the cell interior[2]. The authors identified two specific receptors involved in this process, CD97 and EMR1, and showed that the binding affinities for CD97 and EMR1 were around 14 and 3 times higher, respectively, for the left-handed enantiomer than for the right-handed enantiomer. This provides an explanation for why the left-handed enantiomer was more efficient at entering the cell than its right-handed counterpart. The authors also found that the left-handed enantiomer was more adept at escaping the lysosome.

Xu and colleagues then established that the cellular response to nanoparticles depends on the NLRP3 inflammasome, a protein complex that produces inflammatory cytokines in response to signals of cellular stress or damage. They found that NLRP3 was activated by the opening of potassium ion channels on the cell surface, leading to the efflux of potassium ions from the cell, a well-established trigger for inflammasome activation[3]. When inflammasome activation was suppressed by pharmacologically inhibiting NLRP3 (ref. 4), the nanoparticles could no longer activate the immune cells. Mouse dendritic cells that were deficient in NLRP3 were unresponsive to both enantiomers, providing further evidence for the role of NLRP3 in the response to nanoparticles.

The response of immune cells to the left- and right-handed enantiomers raises the question of whether these gold nanoparticles could be used as adjuvants — compounds that increase the efficacy of a vaccine by providing a stimulus for the immune system. The adjuvant potential of the two enantiomers was tested alongside alum, the current conventional vaccine adjuvant for a common model of influenza virus infection. The left-handed enantiomer was more effective at inducing antibodies against influenza virus than was the right-handed enantiomer, and its effect even surpassed that of alum.

Although the concept of chirality is a common consideration in the design of pharmaceuticals, Xu and colleagues' work is the first to show that the chiral enantiomers of nanoparticles induce different immune responses. Chiral nanoparticles might enhance the efficacy of existing vaccine formulations. Indeed, lipid nanoparticles are already used in messenger RNA COVID-19 vaccines, and are known to have adjuvant actvity[5], but their predominant role[6] in this context is to act as protective droplets to prevent degradation of the mRNA.

Nanoparticles could perhaps provide a dual benefit in improving both vaccine delivery and vaccine efficacy. Nanoparticle-mediated NLRP3 activation would also strengthen the argument for their potential use as adjuvants, because inflammasome activation has previously been shown to contribute to the efficacy of existing adjuvants[7]. However, NLRP3 activation might also lead to detrimental inflammatory responses, and so its role here might inform studies into the possible toxicity of nanoparticles.

As the use of nanoparticles in various settings increases — for example, in the production of cosmetics, textiles and electronics — so, too, does our everyday exposure to them. Although some nanoparticles can alter the healthy function of immune cells, or cause immune suppression[8], others can stimulate the immune system[9], including those reported here. Such nanoparticles might prove beneficial in augmenting immune responses to improve vaccine efficacy or even cancer immunotherapy. As Xu and co-workers' study shows, chirality is a key property of nanoparticles in immune-cell activation — a discovery that will no doubt inform efforts to design nanoparticles with widespread utility.

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Climate science

Future ice loss captured by historical snapshots

Twila A. Moon

Archival images of glacial ice on a Norwegian archipelago, together with the islands' climatic diversity, enable application of an innovative method for making long-term projections of ice loss using short-term observations. **See p.374**

Melting glaciers, ice caps and ice sheets are wreaking havoc at shorelines around the world, and there is widespread recognition of the need to understand where, when and how much ice will be lost in the future as a result of climate change. Much of what we know about Earth's existing land ice is gleaned from rich remote-sensing records, yet relatively few of these records span more than a couple of decades — time periods that are short enough to be biased by sporadic glacier behaviour. On page 374, Geyman *et al.*[1] use observations of glaciers on the Norwegian islands that make up Svalbard to improve projections of the ice mass that is expected to be lost in this area during the twenty-first century.

The team borrowed a method, known as space-for-time substitution, that is commonly used in other long-timescale research fields[2]. It takes advantage of the fact that Svalbard's relatively small land mass contains more than 1,500 glaciers across a range of climate zones. Ideally, scientists would study a single glacier — Glacier X — over hundreds of years to unravel how it responds to climate changes. Instead, Geyman *et al.* studied hundreds of glaciers over shorter timespans, with the requirement that these glaciers exist over a wide range of climate zones — from the colder climate that Glacier X experienced in the past to the warmer climate that the glacier will face in the future. In this way, the authors used climate variation in space as a substitute for climate variation over time.

The space-for-time substitution method can run into road blocks if the observational timescale is too short to avoid sporadic variability. Some glaciers can undergo brief, rapid surges of ice motion, and a few of these surging glaciers could derail a ten-year record, falsely suggesting rapid mass loss for a particular climate zone. Geyman *et al.* overcame this challenge with the help of more than 5,500 aerial photographs that had been taken from a scout aeroplane in 1936 and 1938, and that were gathering archival dust. Even readers who gloss over the study details will be astounded by the image comparisons that accompany the research.

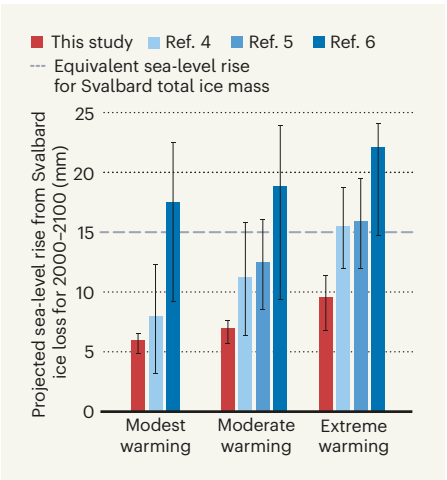

Figure 1 | Projections for twenty-first-century ice loss on Svalbard. Geyman *et al.*[1] estimated, on the basis of three scenarios used by the Intergovernmental Panel on Climate Change[3], that future ice loss on the Norwegian archipelago of Svalbard will be more moderate than projections reported in previous studies. Ice mass loss is measured by the equivalent rise in sea level (in millimetres), and values from the present study are compared with previously reported values (refs 4–6). The dashed line indicates the equivalent sea-level rise that Geyman and colleagues estimated for loss of all Svalbard glaciers, which represents an upper limit on possible ice loss. The projected loss will still have serious global consequences requiring mitigation, and the result does not change other global ice-loss projections. (Adapted from Fig. S7 of ref. 1.)

These aerial images allowed Geyman *et al.* to painstakingly recreate a digital elevation model for Svalbard in the 1930s. The authors then compared this reconstructed ice surface with modern elevation models to extract a record of Svalbard-glacier mass change spanning more than seven decades — long enough to suppress most short-term variability caused by glacier dynamics.

Using their record of the ice lost since the 1930s, Geyman and colleagues found a strong linear relationship between mean summer temperature and change in glacier surface elevation across the whole of Svalbard. They then used the space-for-time method to predict future changes in glacier surface elevation, and converted these estimates into mass changes. By testing three warming scenarios used by the Intergovernmental Panel on Climate Change[3], ranging from modest to extreme warming, the authors project twenty-first-century glacier thinning rates that are at least double the 1936–2010 rates.

Applying a linear relationship between mean summer temperature and glacier thinning does not take into account any future lengthening of the summer melt season — a development that seems likely. By introducing an alternative method that accounts for a lengthening melt season, Geyman *et al.* found that their projections change substantially (with increased ice loss) for only the most extreme warming scenario. Fortunately, current global climate pledges, if realized, are expected to limit warming to below this level, for which the linear relationship suffices (see go.nature.com/3cn3ppk).

Geyman and colleagues are also not able to fully explore the potential implications of changes in amplified near-surface air temperature at the poles, relative to the rest of the planet. This Arctic amplification is especially strong in winter, so that Arctic winters are warming more rapidly than Arctic summers. As a result, observational records thus far show a wider temperature variation between seasons than is expected in the future[4], and projected decreases in this inter-seasonal variation might have unconsidered consequences for mass loss.

The work by Geyman *et al.* paints a different picture of future ice loss from that of previous studies[5–7], almost all of which projected that more ice would be lost during the twenty-first century than Geyman *et al.* estimate, and which included values that now seem to be unrealistic (Fig. 1). These unrealistic values are highlighted by the authors' estimation of the total volume of ice on Svalbard using an ice-free surface-topography data set published previously[8]. The volume they calculated would be equivalent to a mean sea-level rise of 15 millimetres if all of the ice mass were lost. Thus, the previous estimates of sea-level rise

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