ingest material to be broken down. These changes correlated with increased microglial uptake of amyloid-β. By contrast, training led to enhancer and gene-expression changes associated with inflammation and energy expenditure.

Could targeting enhancer activity be a way of regulating immune memory in the brain, thereby altering the progress of neurological disorders? Enhancer activation is modulated by histone deacetylase (HDAC) enzymes, and the authors found that the loss of HDAC2 in microglia blocked immune training in these cells in healthy mice. Reduction of HDAC2 levels in neurons has been shown to improve memory and reverse gene-expression changes induced by neurodegeneration[11]. Furthermore, loss of HDAC1 and HDAC2 in microglia reduces amyloid-β levels and improves memory in a different mouse model of Alzheimer's disease[12]. An appealing possibility is that HDAC2 inhibition blocks microglial immune training and enhances the cells' ability to clear amyloid-β in people with Alzheimer's disease. However, regulating immune memory in the brain without causing deleterious consequences in the rest of the body will be challenging.

This work also opens up other avenues for research. For instance, metabolic products are often required for the activity of enzymes that regulate enhancers. Perhaps changes in metabolism mediate and perpetuate enhancer activation in microglia. Whether this is the case, and how specific enhancers are then targeted for training or tolerance, remains unknown.

The mechanism by which immune memory is transmitted to the brain from the periphery is also unknown. One possibility, suggested by Wendeln *et al.*, is that inflammatory molecules are transported to the brain through the blood. Alternatively, peripheral immune cells might infiltrate the brain and activate microglia, or peripheral nerves might send signals to indicate that inflammation has occurred. One such possible neuronal pathway is the gut–brain axis, through which gut microbes can modulate microglial behaviour[13].

The authors focused on microglia, but other cell types in the brain probably also contribute to the effects of training and tolerance. For example, cells called astrocytes, which have immunomodulatory functions, are activated during Alzheimer's disease[14]. The researchers showed that there were fewer activated astrocytes in APP23 mice exposed to either one or four doses of LPS than there were in untreated APP23 mice. This difference might be driven by microglia-derived factors[15] — but another explanation is that astrocytes, which can detect inflammatory signals[14], also retain a memory of previous stimuli. These possibilities still need to be tested.

Although rapid progress has been made in identifying genetic contributions to neurological disorders, environmental factors also have substantial effects. Because of this, Wendeln and co-workers' findings will be of broad interest. In addition to changes due to infections, the innate immune system can be influenced by environmental stimuli such as stress. Stress has been linked to neurological disorders, and an effect of stress on innate immune training has been hypothesized but remains unexplored in the context of these diseases[16].

Finally, blocking immune training or mimicking immune tolerance in the brain will be of therapeutic benefit only if the current findings are replicated in humans. Demonstrating microglial immune memory in humans will be difficult, owing to the inaccessibility of brain tissue in living people. However, analysis of inflammatory signalling molecules released into the cerebrospinal fluid could be used as a proxy for microglial immune memory. Regardless of the immediate therapeutic potential, Wendeln and colleagues' work sets the stage for further investigation of the impact of environmental factors on microglial function in neurodegenerative conditions. ■

Alexi Nott *and* **Christopher K. Glass** *are in the Department of Cellular and Molecular Medicine, University of California, San Diego, San Diego, California 92093, USA.* **C.K.G.** *is also in the Department of Medicine, University of California, San Diego.*
e-mail: ckg@ucsd.edu

1. Netea, M. G., Latz, E., Mills, K. H. G. & O'Neill, L. A. J. *Nature Immunol.* **16**, 675–679 (2015).
2. Netea, M. G. *et al. Science* **352**, aaf1098 (2016).
3. Wendeln, A.-C. *et al. Nature* **556**, 332–338 (2018).
4. Labzin, L. I., Heneka, M. T. & Latz, E. *Annu. Rev. Med.* **69**, 437–449 (2018).
5. Sturchler-Pierrat, C. *et al. Proc. Natl Acad. Sci. USA* **94**, 13287–13292 (1997).
6. Kaufmann, E. *et al. Cell* **172**, 176–190 (2018).
7. Mitroulis, I. *et al. Cell* **172**, 147–161 (2018).
8. Christ, A. *et al. Cell* **172**, 162–175 (2018).
9. Füger, P. *et al. Nature Neurosci.* **20**, 1371–1376 (2017).
10. Ostuni, R. *et al. Cell* **152**, 157–171 (2013).
11. Gräff, J. *et al. Nature* **483**, 222–226 (2012).
12. Datta, M. *et al. Immunity* **48**, 514–529 (2018).
13. Erny, D. *et al. Nature Neurosci.* **18**, 965–977 (2015).
14. Sofroniew, M. V. *Nature Rev. Neurosci.* **16**, 249–263 (2015).
15. Liddelow, S. A. *et al. Nature* **541**, 481–487 (2017).
16. Salam, A. P., Borsini, A. & Zunszain, P. A. *Mol. Psychiatry* **23**, 170–176 (2018).

This article was published online on 11 April 2018.

NANOSCIENCE

A peptide-guided twist of light

The growth of gold nanoparticles has been manipulated using amino acids and peptides to produce twisted structures that alter the rotation of light. The method could simplify the development of optical devices. SEE LETTER P.360

GUILLERMO GONZÁLEZ-RUBIO & LUIS M. LIZ-MARZÁN

Nanoparticles that control the rotation of light have potential applications, for example in optical devices[1] and sensors[2], but preparing such particles has been difficult, especially from crystalline metals. On page 360, Lee *et al.*[3] report a remarkable method that uses amino acids or peptides (small molecules formed from amino acids) to direct the dissymmetric growth of gold nanoparticles that have a twisted morphology. The findings open up radical opportunities for the preparation of materials and devices that control light rotation.

Dissymmetric objects that cannot be superimposed on their mirror image are found at a variety of scales and include molecules of DNA, snail shells and even galaxies. Such structures are said to be chiral. Louis Pasteur coined the concept of molecular dissymmetry in 1848, when he attributed the morphological differences in crystals of tartrate to the existence of mirror-image tartrate molecules[4,5]. We now know that the functions of biomolecules often depend on chirality, which, for example, provides the basis of exquisitely specific interactions between enzymes and their substrate molecules, enabling the proper functioning of living organisms.

One property of chiral molecules is that each mirror-image form interacts differently with circularly polarized light (in which the electric field traces a helix in the direction of the light's propagation), resulting in phenomena known collectively as optical activity. For example, circular dichroism involves the differential absorption of left- and right-handed circularly polarized light by the mirror-image forms of a molecule. The optical activity of chiral organic molecules has been used to manipulate the rotation of light, but almost invariably in the ultraviolet region of the electromagnetic spectrum.

In the past decade, some inorganic materials have also been shown to have chirality and optical activity[6], thereby enabling control of the rotary propagation of light to be extended to the visible and near-infrared regions. Prominent among these inorganic compounds are nanostructured materials that

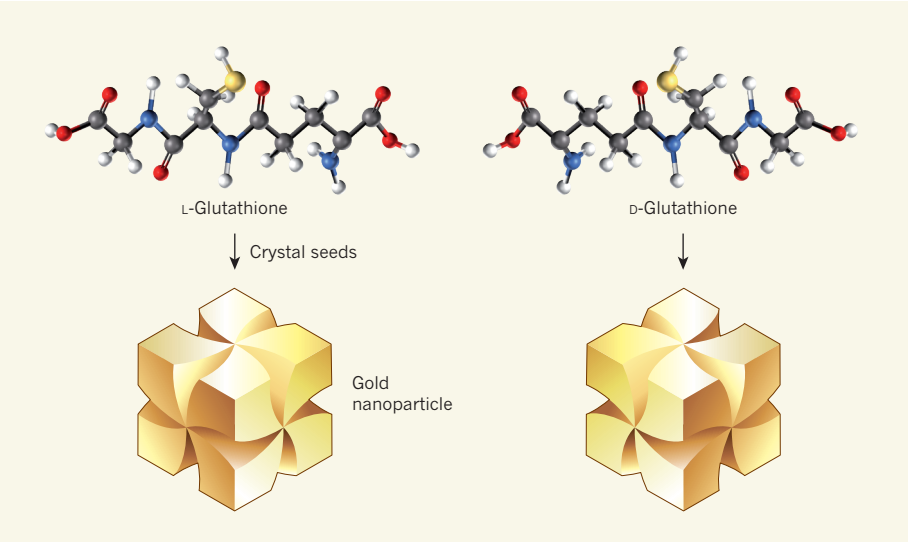

Figure 1 | The transfer of chirality from peptides to nanoparticles. Lee *et al.*[3] grew gold nanoparticles from crystal 'seeds' in the presence of chiral amino acids or peptides, which can exist as mirror-image forms. The resulting nanoparticles were also chiral, and the mirror-image form that grew depended on the form of the amino-acid or peptide additive that was used. For example, the peptide glutathione can occur as mirror-image L- and D-isomers, which direct the growth of mirror-image versions of the helicoid-shaped nanoparticle shown. (Glutathione structures from Guillermo González-Rubio.)

exhibit plasmonic effects. Such effects derive from the oscillations of conduction electrons in nanostructured metals or in other materials that contain free electrons, and result in the extremely efficient absorption and scattering of visible and near-infrared light. The wavelength involved is defined by the composition, dimensions and morphology of the nanomaterial.

The use of chiral plasmonic effects has been identified as one of the most promising routes to developing optical metamaterials — artificial structures such as 'invisibility cloaks'[7] with optical properties that differ from those of materials found in nature. This has motivated considerable effort towards the fabrication of nanoscale objects that have chiral geometry. Substantial advances have been achieved[1] both through top-down fabrication methods, in which nanoscale objects are prepared from bulk materials, and through bottom-up methods, in which the objects are grown using chemical processes.

Top-down approaches can already be used to make small quantities of nanomaterials that have well defined morphologies, but it might be difficult to scale up these approaches to produce the amounts that will be needed for processing into materials or integration into devices. By contrast, bottom-up approaches are typically based on chemistry performed in solution, which is easier to scale up.

Remarkable advances have been made in the scaling up of bottom-up methods to make chiral nanomaterials, mainly by using a chiral template to direct the assembly of preformed nanoparticles. Beautiful examples of such materials include gold spheres adsorbed onto DNA strands[8], gold nanorods interleaved with accurately programmed DNA-origami structures[9] and gold nanorods adsorbed onto helical protein fibres[2]. But in all of these cases, the optical activity obtained is the result of collective plasmonic effects, and the wavelength at which circular dichroism occurs is defined both by the specific properties of the individual building blocks used and by their organization on the template. This means that several parameters must be manipulated to achieve a specific optical effect.

A simpler alternative for generating optical effects would be to grow chiral plasmonic nanoparticles in a way that ensures that all such particles have the same morphology and, therefore, identical optical activities. This can be achieved by using preformed nanoparticles as 'seeds', which are then grown to the desired size and shape by the slow precipitation of material onto them, typically using additive molecules to direct the growth process[10]. Such methods have been used to make highly symmetric metallic nanoscale objects, including spheres, rods and octahedra. This approach has also been used to make chiral structures from certain inorganic materials[11], but not from metals such as gold that have a highly symmetric crystalline structure. Lee *et al.* now report an advance that fills this methodological gap.

"The nanomaterials could be processed into composite materials, and might find technological applications."

The main breakthrough that the authors report is the use of chiral amino acids or peptides that contain thiol (SH) groups as additives in the seeded growth of gold nanoparticles (Fig. 1). These additives affect the growth rate of certain crystal facets, which leads to the formation of nanostructures that have intricate chiral morphologies and an impressive degree of monodispersity — all particles are highly similar in size and shape. Moreover, the obtained morphology can be manipulated by varying either the structure of the shape-directing molecule or the initial shape of the seed particles.

Lee and colleagues therefore demonstrate that the chirality and optical behaviour of naturally occurring amino acids and peptides can be transferred to shaped plasmonic nanocrystals. The resulting high-quality, chiral gold nanoparticles (see scanning electron microscopy images in Fig. 1 of ref. 3) show strong circular dichroism (a large difference between the absorption of left- and right-handed circularly polarized light), with the wavelength and intensity of the signal determined by the nanoparticles' specific morphology. Because this remarkable optical response arises from intrinsic single-particle effects, the nanomaterials could be processed into composite materials or thin films, and might even find technological applications through incorporation into devices.

The authors' procedure is a remarkably simple modification of methods that are commonly used to grow shaped gold, silver or palladium nanoparticles. It is therefore likely to be readily adopted to produce chiral nanostructures of these 'noble' metals, which have improved catalytic or electronic properties compared with analogous non-chiral structures. The success of the technique will depend on whether it does indeed work for noble metals other than gold, and whether the small, naturally occurring chiral additives can be replaced by synthetic dissymmetric molecules. Further studies are needed to determine how the process is affected by the growth kinetics of particles, by the strength of the interactions between the nanocrystal surface and the chiral additive, and by the composition and size of the seeds. ■

Guillermo González-Rubio *and* **Luis M. Liz-Marzán** *are at CIC biomaGUNE, 20014 Donostia-San Sebastián, Spain.* **L.M.L.-M.** *is also at Ikerbasque, Basque Foundation for Science, Bilbao, Spain.*
e-mail: llizmarzan@cicbiomagune.es

1. Hentschel, M., Schäferling, M., Duan, X., Giessen, H. & Liu, N. *Sci. Adv.* **3**, e1602735 (2017).
2. Kumar, J. *et al. Proc. Natl Acad. Sci. USA* **115**, 3225–3230 (2018).
3. Lee, H.-E. *et al. Nature* **556**, 360–365 (2018).
4. Pasteur, L. *Ann. Chim. Phys. Sér. 3* **24**, 442–459 (1848).
5. Gal, J. *Nature Chem.* **9**, 604–605 (2017).
6. Ma, W. *et al. Chem. Rev.* **117**, 8041–8093 (2017).
7. Pendry, J. B. *Science* **306**, 1353–1355 (2004).
8. Kuzyk, A. *et al. Nature* **483**, 311–314 (2012).
9. Lan, X. *et al. J. Am. Chem. Soc.* **137**, 457–462 (2015).
10. Liz-Marzán, L. M. & Grzelczak, M. *Science* **356**, 1120–1121 (2017).
11. Zhou, Y., Yang, M., Sun, K., Tang, Z. & Kotov, N. A. *J. Am. Chem. Soc.* **132**, 6006–6013 (2010).