the drug specifically stabilizes eIF2Bδ from thermal denaturation (*3*).

How ISRIB enhances eIF2B activity remains unknown. The drug exhibits twofold rotational symmetry, and both the spacing and orientation of its distal aromatic rings are crucial for potency. The results of structure-activity relationship studies by Sidrauski *et al.* suggest that the two halves of the drug make similar interactions with their target, as the same modifications of the two aromatic rings had additive effects on activity (*3*). As eIF2B forms a dimer of heteropentamers (*9*, *10*), the stereochemical properties of ISRIB could be explained if it engages chemically similar moieties symmetrically arranged across the dimer interface. Indeed, Sidrauski *et al.* found that ISRIB promotes formation of eIF2B dimers in vitro (3). Although this could account for the stimulatory effect of ISRIB on GEF activity, there is no direct evidence that dimerization is crucial for activity. The drug also increased association of eIF2Bα with the other eIF2B subunits, which might enhance GEF activity (*11*) independent of eIF2Bα's role in dimerization (*10*).

There is strong evidence that eIF2α phosphorylation and the integrated stress response are important regulators of hippocampal synaptic plasticity, with dual effects of inducing long-term depression while suppressing long-term potentiation and the different types of learning associated with each phenomenon. By dampening the integrated stress response, ISRIB impedes long-term depression that is induced by metabotropic glutamate receptors and a specific type of learning in the mouse (*12*). By contrast, ISRIB or genetic ablation of constituents of the integrated stress response enhances memory in a learning paradigm in the mouse that requires long-term potentiation (*1*, *13*). By establishing that ISRIB acts directly on a key component of the integrated stress response, the new findings should encourage investigation of whether ISRIB, or related compounds with this mode of action, are useful for treating cognitive disorders in humans. ■

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SHAPE-MEMORY ALLOYS

Taming the temperamental metal transformation

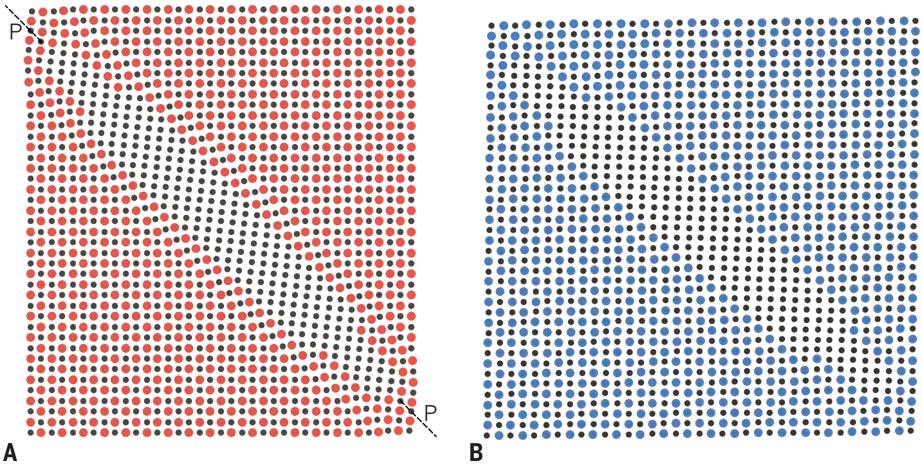
An alloy can undergo millions of cycles of shape changes in response to stress jumps

By **Richard D. James**

One of the most delightful scientific demonstrations is the shape-memory effect in binary nickel-titanium (NiTi): Stretch out a spring of this alloy so it is apparently permanently deformed, drop it into a cup of hot coffee, and it literally jumps back to its original shape (*1*). However, looks can be deceiving. Repeat performances are limited—especially if the spring had to lift a weight while recovering—because failure by fracture would occur after a few thousand cycles. Also, the temperature at which the spring recovers can change by 10°C after the first few cycles. These effects are believed to be the result of progressive damage in the material as it goes through a large solid-to-solid first-order phase transformation (one requiring heating or cooling) that underlies the shape-memory effect. Thus, it comes as a breathtaking development that, on page 1004 of this issue, Chluba *et al.* (*2*) demonstrate 10 million cycles with nearly exact repeatability of a comparable phase transformation under the exceedingly demanding conditions of full stress-induced transformation.

Applied scientists have largely avoided using shape-memory alloys because of these reliability issues, but slightly Ni-rich NiTi has been a technological success in medical devices such as stents (in excess of $5 billion worldwide) by taking advantage of the related stress-induced transformation. Note that for the shape-memory effect, the alloy returns to its original shape after heating, whereas during stress-induced transformation, it recovers the original shape when the loading force is removed.

These applications are successful because only a one-time full transformation cycle is needed (or at most a few cycles), and NiTi is generally reliable under the very small strains needed. In the case of stents, this one-time cycle consists of severely deforming the cylindrical stent to a tiny radius, inserting it into a small plastic tube at the end of a guide wire, and then deploying it out of the tube with a cleverly designed mechanism once inside the human body. The transformation temperature T_c in NiTi (which is easily modified



Staying aligned. A possible realization of the idea of Chluba *et al.* for decreasing fatigue in shape-memory alloys. Under the cofactor conditions satisfied by their alloy $Ti_{54.7}Ni_{30.7}Cu_{12.3}Co_{2.3}$, there are planes that undergo no distortion by the shape-memory transformation. One of these planes, designated P-P, is shown schematically in (**A**). Despite the large deformation caused by the transformation to martensite (**B**), the flattened precipitate that forms undergoes pure rotation and remains epitaxial (the matching uncolored regions in both panels remain aligned), which eases the transformation. These precipitates nevertheless are available to pin lattice dislocations, which leads to substantial strengthening.

Potential uses of multimillion-cycle phase transformation materials

TECHNOLOGY	PROPERTIES SWITCHED	APPLICATIONS
Actuation	Shape-memory effect	Medical and automotive actuators Remote field-induced cycling of in vivo devices
Sensing	Magnetoelectric properties	Variety of mechanical, electrical, and magnetic sensors
	Dielectric tensor	Optical sensors and smart windows
	Susceptibility	Power electronics
Information storage	Magnetoelectric properties	Magnetic element switching by focused electric fields
Switching	Multiferroic properties	Variety of electromagnetic and optical switches
Solid-state refrigeration	Magnetization	Magnetocaloric effect
	Polarization	Electrocaloric effect
Direct energy conversion	Magnetization	Solar or thermal heat-to-electricity conversion
	Polarization	Waste heat conversion in digital devices; powering spacecraft

by minor compositional changes) governs which effect can be used. Shape memory occurs when T_c is above room temperature, whereas stress-induced transformation occurs when T_c is below room temperature and involves no heating.

For decades, putting the shape-memory effect "to work" has been a tantalizing prospect for researchers. In one full shape-memory cycle, the work output per volume of a NiTi wire is enormous (*3*). When lifting a weight during the "return" phase of the shape-memory effect, the wire can sustain a huge stress of 500 MPa while undergoing a contraction of 5%. Typically, such demanding conditions will lead to failure after only about 10 cycles. By comparison, the strain of the alloy $Ti_{54.7}Ni_{30.7}Cu_{12.3}Co_{2.3}$ found by Chluba *et al.* is smaller, 1.5 to 2.0%, and the maximum stress in each cycle is 400 MPa. However, this strain is appreciable, and 400 MPa is a very large stress—twice the yield stress of a typical structural steel used in building construction—and such high values should transfer to actuation via the shape-memory effect.

What is most interesting about this alloy is that the emerging scientific strategy that underlies its discovery may be transferable to other alloy systems. This alloy closely satisfies the cofactor conditions, mathematical relations among the lattice parameters of the two phases that were derived on the basis of purely theoretical considerations (*4*) [it is the second alloy satisfying these conditions, the first being $Zn_{45}Au_{30}Cu_{25}$ (*5*)]. If the cofactor conditions are satisfied, there is a remarkable degree of fitting between phases. Apparently, the plethora of low-energy microstructures, possible under the cofactor conditions, plays an important role in the repeatability of the transformation.

However, satisfaction of the cofactor conditions is not the whole story. The highly nonstoichiometric composition $Ti_{54.7}Ni_{30.7}Cu_{12.3}Co_{2.3}$ leads to the formation of near-stoichiometric Ti_2Cu precipitates. Despite the large strains, these precipitates have an approximate epitaxial relation to both phases (see the figure). This relation evokes the original strategy of the 1960s that led to the slightly Ni-rich $Ni_{50.6}Ti_{49.4}$ often used today. This alloy supports Ni_4Ti_3 near-epitaxial precipitates that strengthen the ordinarily soft high-temperature phase, leading to an improved (but far from perfect) shape-memory effect in $Ni_{50.6}Ti_{49.4}$.

> ***"For decades, putting the shape-memory effect 'to work' has been a tantalizing prospect for researchers."***

One consequence of the cofactor conditions is the presence of planes in the crystal lattice of one phase that are transformed without distortion to the other phase. Could it be that a family of flattened precipitates aligned with these planes can lead to strengthening and still not impede the transformation? Although the general picture is now clearer, we still have much to learn about the relation between conditions of compatibility and subtle processing steps that yield alloy-strengthening precipitates.

What is on the horizon is quite unrelated to the NiTi system but involves a variety of alloys that not only have a large first-order phase transformation but also exhibit "ferroic" properties—ferromagnetism or ferroelectricity (*6*, *7*)—as well as ferroelasticity. Phase transformations can lead to a strong multiferroic response because ferroelectricity and ferromagnetism are highly sensitive to lattice parameters, which undergo large changes at a phase transformation. Thus, a material can transform from strongly magnetic to nonmagnetic just by heating and cooling a few degrees, and phase transformations could also switch transport and optical properties. Furthermore, the presence of latent heat may allow for direct conversion of heat into electricity.

The coupling of elasticity, electricity, magnetism, and temperature creates many possibilities for sensors, actuators, microelectronic and optical devices, information storage media, magneto-electro-caloric technology, and energy conversion devices (see the table). Materials are likely to emerge from this strategy of multiferroism by phase transformation (*8*, *9*) that could satisfy strong conditions of compatibility between phases, together with appropriate strengthening mechanisms via controlled precipitation. ■

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