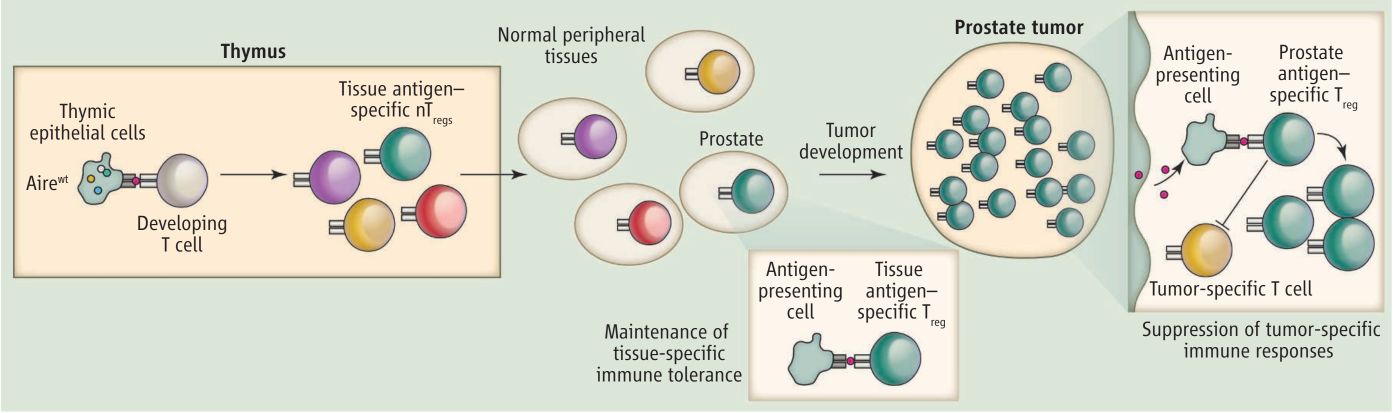


Tissue-specific T$_{regs}$ suppress tumor-specific immune responses. In the thymus, specialized epithelial cells help generate "tissue-specific" T$_{regs}$ with TCRs that recognize specific self antigens. After leaving the thymus, these T$_{regs}$ preferentially accumulate in peripheral tissues according to tissue-restricted expression of self antigens. If a tumor develops, these T$_{regs}$ infiltrate the developing tumor and inhibit tumor-specific immune responses.

evant antigen. These data suggest a model in which populations of tissue-specific T$_{regs}$ arise during thymic development and then accumulate within those peripheral tissues on the basis of antigen recognition (see the figure). As tumors develop, these preexisting tissue-resident T$_{regs}$ are recruited into and/or expanded within the tumor microenvironment, potentially allowing them to exert local immunosuppression. Thus, recognition of tissue-restricted antigens can play a central role in T$_{reg}$ infiltration into tumors (and likely their function), even though the T$_{regs}$ and antigens exist independent of tumor formation.

This study raises additional questions that bear on the role of T$_{regs}$ and cancer development. For example, it would be interesting to know whether the tissue-specific T$_{regs}$ found in the prostate tumor actively suppress antitumor immune responses. Likewise, what is their function in non–tumor-bearing animals? Given that this study makes a convincing case for tissue-resident T$_{regs}$ in this genetically engineered mouse model of prostate cancer, are these findings generalizable to other tumor types and settings? In particular, it will be important to test whether natural, tissue-specific T$_{regs}$ are the predominant population in tumors derived from other tissues and in tumors with higher mutation rates (i.e., carrying more tumor neoantigens) or increased expression of tumor-specific antigens. Indeed, previous work suggested that tumor-infiltrating T$_{reg}$ populations would be a mixture of cells specific for tumor-specific neoantigens and tumor-associated antigens (*7*, *8*). It will also be interesting to determine whether T$_{regs}$ that infiltrate distant metastases are specific for antigens expressed in the original tumor tissue or the tissue in which the metastasis seeded. Metastatic disease accounts for more than 80% of all cancer deaths, so therapies that target T$_{regs}$ in both metastases and primary tumors will likely be more efficacious in treating disease. Understanding the broader set of mechanisms that govern the localization and function of T$_{regs}$ in cancer will help guide the development of appropriate therapies that target this important class of cells in cancer patients.

References

1. D. M. Pardoll, *Nat. Rev. Cancer* **12**, 252 (2012).
2. S. P. Kerkar, N. P. Restifo, *Cancer Res.* **72**, 3125 (2012).
3. S. Malchow *et al.*, *Science* **339**, 1219 (2013).
4. O. J. Finn, *N. Engl. J. Med.* **358**, 2704 (2008).
5. C. S. Hsieh, H. M. Lee, C. W. Lio, *Nat. Rev. Immunol.* **12**, 157 (2012).
6. S. Z. Josefowicz, L. F. Lu, A. Y. Rudensky, *Annu. Rev. Immunol.* **30**, 531 (2012).
7. H. Y. Wang *et al.*, *Immunity* **20**, 107 (2004).
8. H. Y. Wang, G. Peng, Z. Guo, E. M. Shevach, R. F. Wang, *J. Immunol.* **174**, 2661 (2005).

10.1126/science.1235528

MATERIALS SCIENCE

Exceptional Properties by Design

A nanocomposite with a unique combination of attributes heralds an era of new possibilities in materials design.

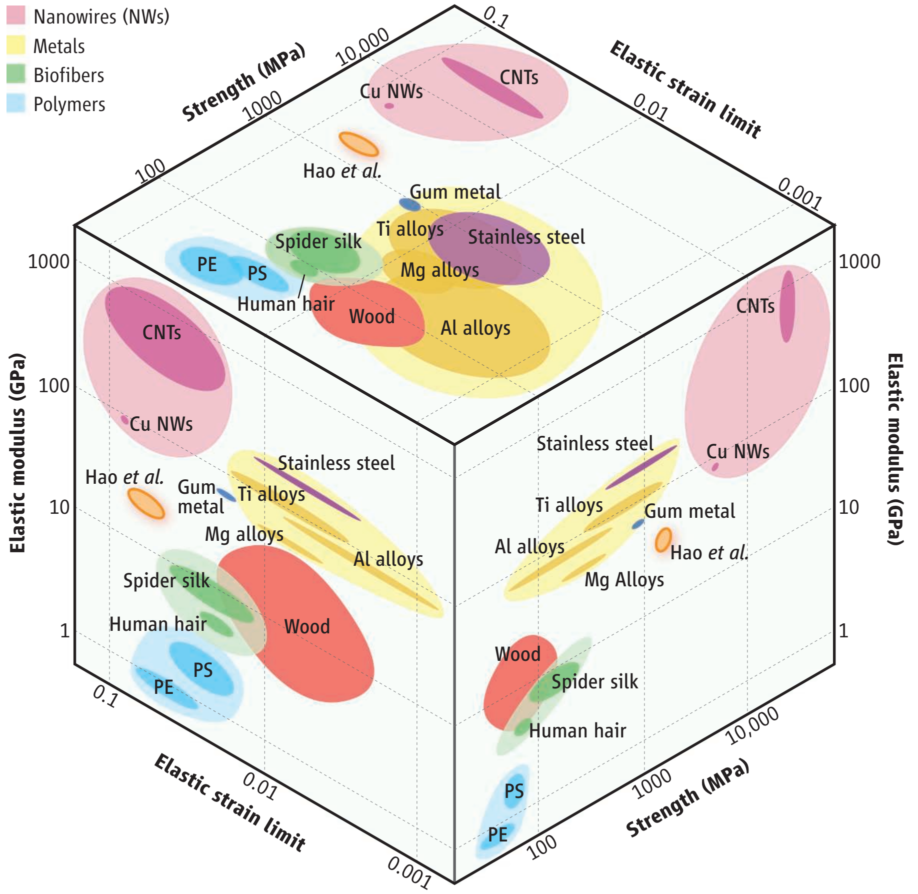
Min Zhou

Materials, be they natural or human-made, come with characteristic combinations of mechanical properties. For example, ceramics have high stiffness but break easily, metals have high strength but limited ability to deform elastically, and polymers can recover from large deformations but carry relatively low stresses. Materials scientists have long tried to make materials that combine desirable properties in unusual ways. One such material is the nanocomposite reported by Hao *et al*. (*1*) on page 1191 of this issue. This material combines high strength, high recoverable strain, low stiffness, and biocompatibility. It may find application in dental braces, cardiac pacemakers, implantable devices, and flexible medical instruments.

Materials scientists and engineers use mechanical property maps (see the figure) to identify materials with particular combinations of attributes (*2*). These maps delineate ranges of accessible properties for bulk materials as well as low-dimensional materials (such as thin films and nanowires). Materials with previously unseen combinations of attributes can be designed by forming composites of different materials. The trick lies in making the constituents work together to yield a desired combination of behaviors. For example, nanowires are strong and have elastic strain limits on the order of 6 to 7%. Large elastic strains

---

School of Mechanical Engineering and School of Materials Science and Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA, and World Class University (WCU) Program on Multiscale Mechanical Design, School of Mechanical and Aerospace Engineering, Seoul National University, Seoul 151-744, Korea. E-mail: min.zhou@gatech.edu



Find the spot. Mechanical property maps allow identification and selection of materials with desired combinations of attributes. The nanocomposite developed by Hao *et al.*, a bulk material consisting of niobium nanowires embedded in a nickel-titanium matrix, falls outside the domain of existing bulk materials and inside the domain of nanowires (see top and left faces of cube). This material is more flexible than other bulk materials with similar strength or stiffness. It may be useful for medical instruments and implantable devices. PE, polyethylene; PS, polystyrene; CNTs, carbon nanotubes.

allow a material to be flexible, adapt to and recover from different shapes, and store and release more energy. These are attractive attributes for sensors, actuators, and flexible devices. However, individual nanowires are too small to be used directly in applications that require bulk materials. How can their exceptional properties be translated into bulk form?

Hao *et al.* approached this challenge by creating a nanostructured composite consisting of niobium (Nb) nanowires embedded in a nickel-titanium (NiTi) matrix. The authors first performed careful calculations of how the nanowires and the matrix deformation can work together and how to condition the residual stresses in the material, and then subjected the material to cycles of stretch and release. This process leaves the Nb nanowires in tension and the NiTi matrix in compression even when the overall material is not under external forces. Thus, when the material is stretched, the matrix merely becomes less compressed or slightly stretched, allowing different parts of the material to deform and recover without the formation of defects (which marks the end of elasticity).

By engineering the structure of the interfaces between the fibers and the matrix at the atomistic level and controlling residual stresses, the authors can take advantage of the large elastic deformations of the nanowires in a bulk material setting, effectively coaxing the pseudoelastic deformation (each cycle of which involves the loss of some energy while the original size and shape of the material are recovered) of the NiTi matrix to go along with the elastic deformation (full recovery of mechanical work as well as size and shape) of the nanowires.

Previous attempts to do this were not successful (*3*). The key is to avoid lattice mismatch and defect generation by involving only coordinated shear deformation of lattices that does not change the relative positions of atoms. The resulting material occupies unique spots in the strength-stiffness, strength–elastic strain limit, and stiffness–elastic strain limit maps of all existing materials (see the figure).

As Hao *et al.*'s results show, design and engineering at the atomistic level can yield new materials with novel and desirable attributes. Can the envelope be pushed farther out to achieve, say, recoverable strains on the order of 15% or more in a bulk material? Such materials would be attractive as shock absorbers and energy storage devices.

Strains of ~6% approach the theoretical elastic limits of metal nanowires (*4*) and metallic glasses (*5*). However, nanowires of various other materials exhibit recoverable strains up to 15% through phase transformations (*6*, *7*) or even 50% through lattice reorientations (*8*, *9*). Taking advantage of these phenomena means that the resulting materials are likely to be pseudoelastic, as is the shape memory NiTi matrix in the Hao *et al.* nanocomposite. Pseudoelasticity would not be an issue for applications such as dental braces and medical implants. In fact, the ability to dissipate energy is required for many applications such as damping.

Materials development has historically been largely a trial-and-error empirical process that is expensive and time-consuming. Laboratory synthesis alone cannot explore material configurations not yet in existence. Computational design through modeling and simulation is making the concept of materials by design a reality (*10*, *11*); integrated computations, synthesis, and experiments are accelerating the development of new materials from the bottom up (*11*, *12*). In the future, we are likely to see more materials that, like the nanocomposite of Hao *et al.*, push the boundaries of possibility.

References and Notes

1. S. Hao *et al.*, *Science* **339**, 1191 (2013).
2. M. F. Ashby, *Materials Selection in Mechanical Design* (Butterworth Heinemann, Amsterdam, 2005).
3. Y. Dzenis, *Science* **319**, 419 (2008).
4. Y. Yue, P. Liu, Z. Zhang, X. Han, E. Ma, *Nano Lett.* **11**, 3151 (2011).
5. L. Tian *et al.*, *Nature Commun.* **609**, 1 (2012).
6. A. J. Kulkarni, M. Zhou, K. Sarasamak, S. Limpijumnong, *Phys. Rev. Lett.* **97**, 105502 (2006).
7. J. Wang *et al.*, *Phys. Rev. B* **76**, 172103 (2007).
8. W. Liang, M. Zhou, F. J. Ke, *Nano Lett.* **5**, 2039 (2005).
9. H. S. Park, K. Gall, J. A. Zimmerman, *Phys. Rev. Lett.* **95**, 255504 (2005).
10. G. B. Olson, *Science* **277**, 1237 (1997).
11. D. L. McDowell, G. B. Olson, *Sci. Modell. Simul.* **15**, 207 (2008).
12. T. E. Jones, M. E. Eberhart, S. Imlay, C. Mackey, G. B. Olson, *Phys. Rev. Lett.* **109**, 125506 (2012).

Acknowledgments: Supported by the NSF Center for Computational Materials Design and the WCU program of Korea. I thank Y. F. Gao, C. J. Lammi, A. Barua, S. Kim, and Y. Li for assistance.

10.1126/science.1236378