The DNA strands on the edges of each shape have free binding domains, which can cause the shapes to clump together. To render the edges non-sticky, the authors added edge-protector strands where necessary. Because each of the four domains on *N* different tiles might need to be protected, a set of 4*N* additional strands was required. So, to access any of 2^N potential shapes, the single-stranded tile technique requires just 5*N* different strands. This efficient and modular architecture allowed Wei *et al.* to construct 107 shapes by hand, spending just a few hours on each shape. By using a robot to select and mix strands, the authors reduced the time required to make a shape to one hour. In this way, they constructed 44 shapes in about 44 hours. This advance truly brings DNA nanotechnology into the rapid-prototyping age, and enables DNA shapes to be tailored to every experiment.

Wei and colleagues' technique is the large-scale realization of a concept known as uniquely addressed tiling, which was first formally described[13] 12 years ago. So why is this advance happening only now? One answer is that, according to the predominant thinking about DNA self-assembly, such a technique should not work well — making the concentrations of tile strands perfectly equal is experimentally difficult, and relatively small departures from equality were expected to result in low yields of target structures. This idea followed from the common assumption that many DNA structures would begin self-assembling simultaneously, and then get stuck as partially complete shapes when tiles present at lower concentrations were exhausted. This potential problem was so compelling that DNA origami was invented expressly to avoid it. But the yields of Wei and colleagues' structures are surprisingly high: up to 40% for some shapes.

The success of the method cries out for explanation. The authors suggest that, if the nucleation of self-assembly is rare and the subsequent growth of a DNA shape is fast, then complete structures will form in preference to partial ones. Another possibility is that more-complete structures can gain strands from less-complete ones through a mechanism called Ostwald ripening, in which strands fall off less-stable structures and rejoin more-stable ones. Wei and colleagues' choice of single DNA strands as tiles — rather than the more complex, multistranded tiles used previously[12] — could have a crucial role, because more-complete structures might steal single strands from less-complete structures directly, without any tiles falling off, by strand displacement.

More generally, both the single-stranded-tile method[1] and DNA origami violate several other previous intuitions about what should and should not work. In both cases, careful studies of yields, kinetics and mechanism will be required to circumscribe the conditions under which each method works best and determine whether the single-stranded tile method will supplant DNA origami in practical applications. Wei and colleagues' findings remind us that we are still just apprentice DNA carpenters, and will embolden others to mix hundreds of DNA strands together against prevailing wisdom. The results will probably surprise us. ■

Paul W. K. Rothemund *is in the Departments of Bioengineering, Computer Science, and Computation & Neural Systems, California Institute of Technology, Pasadena, California 91125, USA.* **Ebbe Sloth Andersen** *is at the Centre for DNA Nanotechnology, Interdisciplinary Nanoscience Center, Department of Molecular Biology and Genetics, Aarhus University, 8000 Aarhus C, Denmark.*
e-mails: pwkr@dna.caltech.edu; esa@inano.au.dk

1. Wei, B., Dai, M. & Yin, P. *Nature* **485,** 623–626 (2012).
2. Seeman, N. C. *J. Theor. Biol.* **99,** 237–247 (1982).
3. Chen, J. & Seeman, N. C. *Nature* **350,** 631–633 (1991).
4. Rothemund, P. W. K. *Nature* **440,** 297–302 (2006).
5. Andersen, E. S. *et al. Nature* **459,** 73–76 (2009).
6. Douglas, S. M. *et al. Nature* **459,** 414–418 (2009).
7. Dietz, H., Douglas, S. M. & Shih, W. M. *Science* **325,** 725–730 (2009).
8. Han, D. *et al. Science* **332,** 342–346 (2011).
9. Maune, H. T. *et al. Nature Nanotechnol.* **5,** 61–66 (2010).
10. Endo, M., Katsuda, Y., Hidaka., K. & Sugiyama, H. *Angew. Chem. Int. Edn* **49,** 9412–9416 (2010).
11. Douglas, S. M. *et al. Science* **335,** 831–834 (2012).
12. Winfree, E., Liu, F., Wenzler, L. A. & Seeman, N. C. *Nature* **394,** 539–544 (1998).
13. Rothemund, P. W. K. & Winfree, E. *Proc. 32nd Annu. Symp. Theor. Comput.* 459–468 (2000).
14. Andersen, E. S. *et al. ACS Nano* **2,** 1213–1218 (2008).

P.W.K.R. declares competing financial interests.
See go.nature.com/tntyxm for details.

REGENERATIVE MEDICINE

Reprogramming the injured heart

When the heart is injured, the muscle does not regenerate and scars are produced. This process can be attenuated in the hearts of live mice by forcing scar-forming cells to become muscle cells. SEE ARTICLES P.593 & P.599

NATHAN J. PALPANT & CHARLES E. MURRY

Cardiovascular disease remains the leading cause of death worldwide. Because of the heart's limited ability to regenerate, injuries such as myocardial infarction (heart attack) heal by scar formation rather than muscle regeneration. As a result, the heart pumps less efficiently, leading to the burgeoning epidemic of heart failure seen today. Current medical therapies support the heart with its reduced function, but scientists and clinicians are eager to learn how to regenerate damaged heart muscle. On pages 593 and 599 of this issue, Qian *et al.*[1] and Song *et al.*[2] describe how, in an effort to improve cardiac function, they have induced scar-forming cells (fibroblasts) to become muscle cells (cardiomyocytes) in the injured hearts of live mice.

The reprogramming of cells from one fate to another moved from the realm of alchemy to biochemistry after the discovery of MYOD1, a transcription factor that regulates the expression of genes involved in the development of skeletal muscle. When experimentally expressed, MYOD1 can convert many cell types into skeletal muscle *in vitro*[3], as well as cells in the injured hearts of live rats[4]. More recently, it was found[5] that somatic (non-germline) cells from adult mammals could be reprogrammed to become pluripotent stem cells — which can differentiate into any cell type — by expressing 'cocktails' of transcription factors. Researchers have recently used this approach to convert differentiated cells directly into other differentiated cell types such as cardiomyocytes[6–10].

Qian *et al.*[1] and Song *et al.*[2] built on previous work[6] which showed that fibroblasts could be reprogrammed into cardiomyocytes *in vitro* by the introduction of genes coding for three transcription factors that regulate heart development (GATA4, MEF2C and TBX5). Qian *et al.* used only these three genes, whereas Song *et al.* observed better *in vitro* reprogramming efficiency by adding a fourth one, which encodes the transcription factor HAND2. In both studies, the authors induced myocardial infarction in mice by occluding a coronary artery (a blood vessel that supplies blood to heart muscle), and used retroviruses to deliver the transcription-factor genes to the injured heart. These viruses can insert genes into the chromosomes of actively dividing cells, such as scar-forming fibroblasts, but not into those of non-dividing cells such as cardiomyocytes. One month after treatment, reprogrammed cardiomyocyte-like cells comprised 2.4–6.5% of the cardiomyocytes in the region bordering the injured area (the infarct border zone) in the study by Song *et al.* and, remarkably, up to 35%

in Qian and colleagues' experiments. Moreover, in both studies, the hearts of treated mice showed improved function compared with those of control mice.

A key challenge for the authors was how to distinguish pre-existing cardiomyocytes from those derived from reprogrammed fibroblasts. To address this, both groups used mice that had been genetically manipulated so that a fluorescent protein was permanently produced only in fibroblasts and their descendants (including those that became cardiomyocytes). The specificity of this lineage-tracing technique depended on the use of certain regulatory sequences, or promoters, that had been taken from genes encoding either periostin or FSP1 — two proteins that are typically produced by fibroblasts, but not cardiomyocytes. In cells in which the promoter was active, a genetic rearrangement led to permanent activation of the gene encoding the fluorescent protein.

Such lineage-tracing approaches are state of the art, but they are not perfect. The biggest pitfall would be activation of the fibroblast promoter in pre-existing cardiomyocytes, so that these would then be mistaken for reprogrammed cells. Neither periostin nor FSP1 is specific to fibroblasts[11,12] (although we know of no evidence for their expression in cardiomyocytes). For these reasons, Song *et al.* carried out further experiments in which they controlled the timing of the fibroblast-marking event using a 'genetic pulse–chase' technique. They report that no cardiomyocytes were marked unless they expressed the transcription-factor cocktail. This finding enhances confidence that true reprogramming had occurred.

Interestingly, both studies found that, although some of the cells had been only partially reprogrammed, others were morphologically and functionally indistinguishable from normal cardiomyocytes. In particular, fibroblast-derived cardiomyocytes in short-term culture were able to contract when stimulated electrically and had electrochemical activities typical of this cell type, including action potentials and electrical coupling. Both research groups used non-invasive diagnostic procedures (echocardiography and magnetic resonance imaging) to identify the improved functional performance and reduced scar area of the treated mice when compared with untreated animals.

The finding of enhanced heart function is certainly important, but how is this happening, and can it be improved on? Although the authors' results suggest that the treatment generated new, functional cardiomyocytes that directly improved pump performance, it is important to remember that the reprogrammed cells constituted only a fraction of the cardiomyocytes in the infarct border zone, which is by nature ill-defined and forms only a fraction of the injured area. Can such a small number of cells directly account for a global increase in heart function? Researchers in stem-cell therapy have encountered similarly disproportionate benefits of cellular grafts in the heart. This therefore raises the possibility that grafted or reprogrammed cells may produce growth factors, cytokines or other signalling molecules that improve the performance of pre-existing cells by enhancing blood flow or cell survival[13].

Going forward, it will be necessary to validate the authors' results in independent labs using different lineage-tracing approaches, and the efficiency of cell reprogramming must be increased. Also, for clinical applications, reprogramming must be achieved without inserting the transcription-factor genes into the fibroblasts' chromosomes, to prevent complications such as malignant transformation. Moreover, are cardiomyocytes the best choice of outcome for reprogramming, or would immature progenitors of cardiomyocytes (which have greater proliferative ability) be better?

Although clinical trials are probably far off, the studies by Qian *et al.* and Song *et al.* open up a new line of investigation in cardiovascular translational medicine. If we can understand the reprogramming mechanisms correctly, regenerative therapy might simply involve inducing the heart to reprogram its own cells after injury. ■

Nathan J. Palpant *and* **Charles E. Murry**
are in the Departments of Pathology, Bioengineering and Medicine/Cardiology, Center for Cardiovascular Biology, Institute for Stem Cell and Regenerative Medicine, University of Washington School of Medicine, Seattle, Washington 98109, USA.
e-mail: murry@uw.edu

1. Qian, L. *et al. Nature* **485,** 593–598 (2012).
2. Song, K. *et al. Nature* **485,** 599–604 (2012).
3. Davis, R. L., Weintraub, H. & Lassar, A. B. *Cell* **51,** 987–1000 (1987).
4. Murry, C. E., Kay, M. A., Bartosek, T., Hauschka, S. D. & Schwartz, S. M. *J. Clin. Invest.* **98,** 2209–2217 (1996).
5. Takahashi, K. & Yamanaka, S. *Cell* **126,** 663–676 (2006).
6. Ieda, M. *et al. Cell* **142,** 375–386 (2010).
7. Pang, Z. P. *et al. Nature* **476,** 220–223 (2011).
8. Vierbuchen, T. *et al. Nature* **463,** 1035–1041 (2010).
9. Szabo, E. *et al. Nature* **468,** 521–526 (2010).
10. Zhou, Q., Brown, J., Kanarek, A., Rajagopal, J. & Melton, D. A. *Nature* **455,** 627–632 (2008).
11. Sen, K. *et al. Am. J. Pathol.* **179,** 1756–1767 (2011).
12. Cheng, J., Wang, Y., Liang, A., Jia, L. & Du, J. *Circ. Res.* **110,** 230–240 (2012).
13. Laflamme, M. A. & Murry, C. E. *Nature* **473,** 326–335 (2011).

EVOLUTIONARY ANTHROPOLOGY

Homo 'incendius'

An analysis of microscopic and spectroscopic features of sediments deposited in a South African cave one million years ago suggests that human ancestors were using fire much earlier than had been thought.

RICHARD G. ROBERTS & MICHAEL I. BIRD

Humans have long been captivated by the flickering flames of the campfire. But when did our ancestors first master the use of fire, and which ancient human species was the first to do so? In *Proceedings of the National Academy of Sciences*, Berna and colleagues[1] report that they have found fragments of burnt bone and ashed plants in one-million-year-old sediments at Wonderwerk Cave, Northern Cape province, South Africa. This evidence of fire occurs in the same sedimentary layers as Acheulian stone tools, usually considered the handiwork of *Homo erectus*. Their discovery more than doubles the accepted antiquity of the habitual use of fire by humans[2,3], and highlights the benefits of using microscopic and molecular techniques to identify 'cryptic combustion' at sites of human occupation — whatever their age*.

Controversy has dogged previous claims for the early use of fire by hominins (primates more closely related to humans than to chimpanzees), such as australopithecines or *H. erectus*. The discovery[4] in the 1940s of apparently charred bones at a 3-million-year-old fossil site in South Africa inspired pioneering Australian palaeoanthropologist Raymond Dart to dub these 'proto-humans' *Australopithecus prometheus* — a new australopithecine species named after the giant in Greek mythology who stole fire from the heavens. However, chemical analysis by English palaeoanthropologist Kenneth Oakley[5] showed that the bones were not burnt, but coated in black oxides of iron and manganese.

Subsequent claims for early fire use have received a similarly cool reception. Some studies have suggested that australopithecines or *H. erectus* had tamed fire by 1.4 million years ago in southern and eastern Africa[6,7], and that cooking has played a pivotal part in the evolution of early *Homo* species[8]. These proposals have been contested, however, either because the burnt remains are not in their original depositional context or because they are found at open-air sites where bush fires ignited by volcanic activity or lightning strikes cannot be ruled out. Acheulian toolmakers were using

*This News & Views article was published online on 23 May 2012.