their fate, during both normal cell turnover and after part of the pancreas was removed to stimulate regeneration.

Surprisingly, the authors found that the percentages of marked β-cells, during both normal turnover and pancreatic regeneration, remained stable, and were not diminished by β-cells arising from insulin-negative progenitors (duct or stem cells; Fig. 1b). In other words, many of the β-cells generated over the study period were marked cells, indicating that they originated from cells that expressed the recombinase at the time the hormone pulse was given — that is, β-cells. The authors' quantification showed that the contribution of non-β-cells — duct or stem cells — was minimal. They also failed to find new, unmarked islets forming during normal β-cell turnover; such unmarked islets would be predicted if other cell types could generate β-cells.

What questions arise from this work? First, the technique that Dor and colleagues used to stimulate pancreas regeneration — partial pancreatic removal — causes acute damage and cellular responses[4]. Their findings are reminiscent of the way in which liver regenerates after partial removal[6,7]. But what happens in models of long-term pancreatic damage[8]? Another question concerning the experiments themselves is whether the recombinase gene used is a little 'leaky', producing some marked non-β-cells that escaped detection and gave rise to marked β-cells. But even if so, these non-β-cells can have given rise only to β-cells: other pancreatic cell types were not marked during regeneration.

With regard to applications of the work, Dor and colleagues' findings raise the prospect of removing β-cells from adult human cadavers, stimulating cell replication, and transplanting the resulting large quantities of β-cells into diabetic patients. This is still a long way off, but the authors' results indicate that research should now focus on the fundamentals of β-cell replication. One question to be addressed is whether human β-cells replicate like mouse β-cells. Human β-cells are known to be able to proliferate, albeit less so than duct cells[9], but the extent to which they can generate new β-cells is unknown. Also, we need to know more about how β-cells interact with other cells in and around the islet, such as blood-vessel cells[10,11].

Another potential source of β-cells for transplantation is human embryonic stem (ES) cells[12]. But if we can generate β-cells from adult β-cells, why contend with ES cells and their associated ethical implications? First, there are insufficient cadaveric β-cell donors. More significantly, ES-derived β-cells are generally 'younger' than cells from cadavers, and so less likely to have accumulated cellular and chromosomal aberrations. Consider, for instance, transplanting β-cells from a 50-year-old cadaver into a diabetic child, and hoping that the cells will remain glucose-responsive and not become carcinogenic over a second human lifespan. Another reason for continuing ES-cell research is that genetic manipulation[13] or therapeutic cloning[14] might eventually be used to ameliorate the recipient's immune intolerance to β-cells.

Nonetheless, given the intense activity in the field of β-cell regeneration, the current focus on adult stem cells, and the early state of ES-cell research, the work of Dor and colleagues[2] can be considered a paradigm shift. It doesn't exclude the possibility that, in some diseases, adult stem cells contribute to the β-cell population. But it does shine light on a resource for insulin-producing cells that has been there all along: the β-cell itself. ■

Ken Zaret is in the Cell and Developmental Biology Program, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, Pennsylvania 19111, USA.
e-mail: zaret@fccc.edu

1. Shapiro, A. M. *N. Engl. J. Med.* **343,** 230–238 (2000).
2. Dor, Y., Brown, J., Martinez, O. I. & Melton, D. A. *Nature* **429,** 41–46 (2004).
3. Butler, A. E. *et al. Diabetes* **52,** 102–110 (2003).
4. Bonner-Weir, S., Baxter, L. A., Schuppin, G. T. & Smith, F. E. *Diabetes* **42,** 1715–1720 (1993).
5. Herrera, P. L. *Development* **127,** 2317–2322 (2000).
6. Rhim, J. A., Sandgren, E. P., Degen, J. L., Palmiter, R. D. & Brinster, R. L. *Science* **263,** 1149–1152 (1994).
7. Overturf, K., al-Dhalimy, M., Ou, C. N., Finegold, M. & Grompe, M. *Am. J. Pathol.* **151,** 1273–1280 (1997).
8. Wang, R. N., Kloppel, G. & Bouwens, L. *Diabetologia* **38,** 1405–1411 (1995).
9. Tyrberg, B., Ustinov, J., Otonkoski, T. & Andersson, A. *Diabetes* **50,** 301–307 (2001).
10. Lammert, E., Cleaver, O. & Melton, D. *Science* **294,** 564–567 (2001).
11. Yoshitomi, H. & Zaret, K. S. *Development* **131,** 807–817 (2004).
12. Thomson, J. A. *et al. Science* **282,** 1145–1147 (1998).
13. Chamberlain, J. R. *et al. Science* **303,** 1198–1201 (2004).
14. Hwang, W. S. *et al. Science* **303,** 1669–1674 (2004).

Biomechanics

Fast fish

Adam P. Summers

Swift-swimming, open-ocean hunters such as mako sharks and tunas need a big engine. Despite their long separation in evolutionary terms, the internal drive systems adopted by these fishes are much the same.

To an underwater observer, mako sharks look a lot like tunas. There is an added *frisson* from the dental battery of the shark, but the two fishes share a common body plan, colour pattern and even swimming style. On page 61 of this issue, Donley and her colleagues[1] demonstrate that, after 400 million years of separate evolutionary trajectories, these two high-speed predators have converged on solutions to the problem of swimming fast that go from skin to skeleton.

Tunas and mackerels, as well as makos and their relatives, appear in the fossil record about 60 million years ago. They roamed the warm Tethys Sea, hunting the newly diversifying radiations of other fishes. Their common ancestor dates back to the Carboniferous, when the bony and cartilaginous fishes diverged[2].

The 'thunniform' body plan is distinctive and has evolved independently several times. The finely streamlined, teardrop-shaped body, with a high-aspect-ratio tail fin and a narrow tail region, is familiar from several speedy denizens of the deep — including dolphins, marlin and makos, and even the extinct ichthyosaurs. Tunas and dolphins also

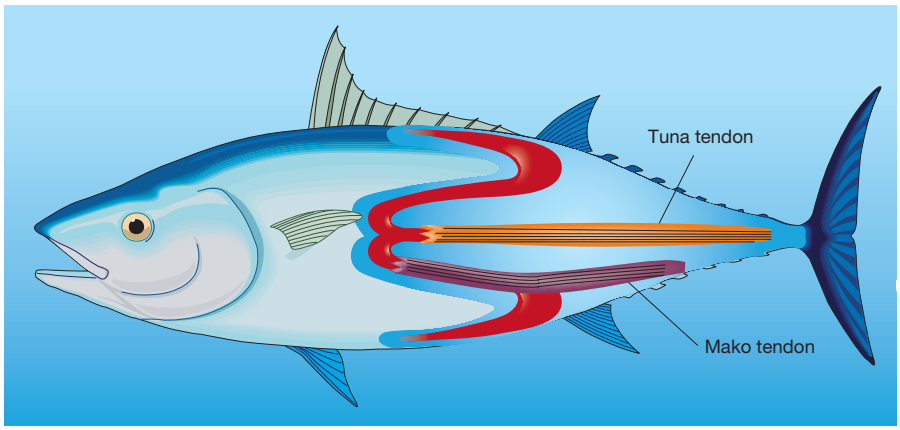

Figure 1 **Marine power transmission. The muscle that propels a fish has a complex three-dimensional structure. The boundaries of each block of muscle are defined by a sheet of connective tissue, which is bent into a zig-zag with two cones of muscle pointing forwards and two pointing backwards. In swift-swimming tunas, power is transmitted by a prominent tendon that arises between the two forward-pointing cones. Donley *et al.*[1] show that a tendon has arisen convergently in the mako shark from the backward-pointing cone of connective tissue.**

share a swimming style; they have lost the whole-body fishy wriggle in favour of a businesslike sweep of the tail that leaves the predatory front end of the body relatively steady. Donley *et al.* show that the mako shark also has this swimming style. This lends support to the hypothesis that thunniform ichthyosaurs swam swiftly, generating thrust with their tail rather than their whole body[3].

Fishes typically have two distinct muscle types on their flanks: a large mass of white muscle and a smaller band of red muscle running the length of the animal just under the skin. Fishes cruise along by throwing their body into waves with alternate contractions of the aerobic, fatigue-resistant red muscle. For short bursts the larger, anaerobic and rapidly fatiguing white muscle is activated.

In both tunas and makos the body muscle mass is shifted well forward, giving them a distinctive broad-shouldered look when viewed from above. The red muscle is also located within the mass of white muscle, nearer the vertebral column, rather than close to the skin. This anatomy allows heat from the continuously activated red muscle to be retained in the core of the fish, leading to local warm-bloodedness.

Shifting the red muscle forward and towards the midline requires modifications of the force-transmission system that drives the tail. As anyone who has picked at a plaice fillet can tell, fish body musculature is divided into a series of blocks with a complex three-dimensional shape. Between each block is a 'myoseptum', a sheet of densely collagenous connective tissue that acts as a sheet of tendon[4].

In most fishes these blocks form a pair of W's, lain on their side and arranged one above the other. In tunas and mackerel the points of the W's are extended into very long tendons that run much of the length of the body and insert on the tail (Fig. 1). The red muscle, acting on these long tendons, transmits its force over a far greater distance than in other fishes[5].

The anatomy of the myosepta of makos is quite different, with a linearly arrayed tendon arising out of one of the legs of the W. This tendon is both distinct and quite long, in some cases reaching 19% of the total length of the animal (Fig. 1). Towards the tail of the fish, these myoseptal tendons converge into a heavy collar of connective tissue. Donley *et al.*[1] show that, despite the difference in shape, mako tendons play an identical role in shifting the force generated by the red muscle mass towards the back end of the fish.

In Donley and colleagues' experiments, mako sharks were allowed to swim in the aquatic version of a treadmill: a broad-bore tube that recirculates water from the tail of the fish to the head, allowing the animal to swim in place. Using sonomicrometry, a technique that involves implanting tiny piezoelectric crystals in the muscle, they measured the shortening of the white and the red muscle fibres.

During passive undulation, when neither muscle type is active, the red and white muscle changed length in perfect lock step. When the mako started swimming actively, requiring activation of the red cruising muscle, there was a clear shift in the timing of shortening. The red muscle shortens well after the white, a shift also seen in tunas. This change in timing means that the red muscle is acting further along the body, causing curvature more towards the tail, while the white muscle causes local curvature changes.

For decades, the similarities between mako sharks and tunas have been the subject of speculation. After all, understanding the mechanisms behind their locomotion could lead to high-speed autonomous underwater vehicles. The data from these two high-speed swimmers seem clearly to endorse a solution that puts as much emphasis on the placement of actuators as on the overall shape of the vehicle. ■

Adam P. Summers is in the Department of Ecology and Evolutionary Biology, 321 Steinhaus Hall, University of California, Irvine, California 92697-2525, USA.
e-mail: asummers@uci.edu

1. Donley, J. M., Sepulveda, C. A., Konstantinidis, P., Gemballa, S. & Shadwick, R. E. *Nature* **429,** 61–65 (2004).
2. Bernal, D., Dickson, K. A., Shadwick, R. E. & Graham, J. B. *Comp. Biochem. Physiol.* **129,** 695–726 (2001).
3. Motani, R. *Nature* **415,** 309–312 (2002).
4. Summers, A. P. & Koob, T. J. *Comp. Biochem. Physiol.* **133,** 1159–1170 (2002).
5. Westneat, M. W., Hoese, W., Pell, C. A. & Wainwright, S. A. *J. Morphol.* **217,** 183–204 (1993).

Earth science

Hot metal

Carl B. Agee

The solubility of oxygen in molten iron increases at high temperature. Could this explain why Earth's mantle is poor in iron oxide, whereas the mantle of Mars, which formed under cooler conditions, is not?

The fate of light elements, such as oxygen, sulphur, carbon and hydrogen, during the formation of planetary cores has been hotly debated for decades. Forty years ago, Birch[1] estimated that about 10% of Earth's core must be made of one or more of the light elements, to account for the density deficit seen in seismic observations when compared with a hypothetical core of pure iron metal. The advent of high-pressure, high-temperature technology in the 1980s has enabled the behaviour and distribution of elements between the mantle and core to be examined under conditions that simulate those in the deep planetary interior. Results from some of the first exploratory experiments[2] suggested that sufficient oxygen would dissolve in iron metal under the extreme pressures at Earth's core–mantle boundary to account for the density deficit.

But Rubie *et al.*[3] have evaluated data on oxygen partitioning between mantle and core materials — from experiments performed by them and others, under extreme conditions[3–5] — and conclude that higher temperatures dramatically increase the amount of oxygen that will dissolve in molten iron metal (page 58 of this issue). In contrast to earlier work, Rubie *et al.* find that pressure has the opposite effect, decreasing the affinity of oxygen for molten iron metal. But if temperature and pressure have opposite effects on oxygen solubility in molten metal, which, if either, wins out in the high-pressure, high-temperature environment of planetary interiors? The deciding factors, it seems, are the size of the planet and the depth of its hypothesized 'magma ocean'.

About four billion years ago, the newly formed Earth and its neighbouring planets were subjected to an intense meteor bombardment — so intense that the collisions might have melted a considerable depth of the fledgling planets' rocky surfaces into oceans of magma. Rubie *et al.*[3] note that if a magma ocean on Earth had occupied a slightly greater volume than that of the modern upper mantle, extending to less than 800 km below the planet's surface, then the magma could only have been as hot as 2,500 K — not hot enough to allow the temperature effect to dominate oxygen solubility. They calculate that temperature would have made a difference only if the magma ocean extended well into the lower mantle, perhaps as deep as 1,800 km, where temperatures need to be 3,500 K or above for rock to melt (Fig. 1, overleaf). This depth of magma ocean is broadly consistent with the trace levels of the siderophile, or 'iron-loving', elements that remain in Earth's mantle today. These elements have been used as geobarometers or thermometers to estimate that the magma ocean was as deep as 1,200 km, with temperatures as high as 3,500 K and pressures of 50 gigapascals at its base[6,7].

How did this hot, deep magma ocean process and transform the primordial material from which the early Earth formed? Imagine building the Earth with a mix of silicates and metal in the proportions found in meteorites; about half of the iron would exist in its metal form and the other half as iron oxide, mostly as a constituent of silicate