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Regrow Your Own

Broken heart? No problem. New liver? Coming right up. The road to regeneration starts here.

By Jennifer Kahn

By the time he was 45, cardiologist Mark Keating had reached the pinnacle of a doctor's career. He was preparing to move from his prestigious post as an investigator at the University of Utah to an even more exalted position as a professor at Harvard. He'd just won three important prizes for his comprehensive work on the genetics of heart arrhythmias. He seemed destined for even more glory in the field of cardiac genetics.

But oddly, Keating couldn't keep his mind off newts. He was particularly obsessed with an obscure species native to East Coast forests: a bandy-legged amphibian with a flat tail, blunt head, and vivid crimson dots. Red-spotted newts are endangered, but that wasn't what lured Keating away from his heart patients. Rather, newts' famous ability to heal themselves fascinated him - they can produce a new eye or sprout a leg if one is amputated, even reconnect a severed spinal cord.

By academic standards, shifting from cardiology to developmental biology is a bizarre career move. Regeneration studies is a backwater even among biologists, who have been chopping the legs off salamanders for more than 200 years without ever discovering why some of them manage to grow back. And while clues to regeneration have emerged - retinoic acid will induce some frogs to grow three new legs in place of one - the field has a history of derailing respectable scientists.

As to whether humans could ever develop similar capacities of self-repair, most biologists have concluded, albeit reluctantly, that the answer is no. There seems to be something inherently different about amphibian cells: a swamp-animal mutability that mammals - including people - simply don't possess.

But Keating remains convinced that newts hold the key to human healing. Our bodies, he points out, can already regenerate to a degree, repairing broken bones and regularly trading dead cells for new ones. Skin cells, for instance, last about two weeks, and our stomach lining molts once a month. This constant replenishment is what enables our 70-year lifespan, but cell growth is calibrated to run at a trickle: too slow to fix major damage. Lose an arm or a kidney and that's it; we can't generate the lost part any more than a car can sprout a new transmission.

Why? It's an evolutionary mystery. The ability to regrow legs and eyes seems like a clear Darwinian advantage - one that surviving generations would have retained. But a paradox of regeneration is that the higher you move up the evolutionary chain, the less likely you'll have the ability to regrow limbs or organs. Keating's mission: figure out the cause of this paradox - and reverse it.

Keating himself believes that regeneration research is on the brink of a revolution - the very place genetics was 20 years ago. "We've been studying regeneration for 200 years, sure," he shrugs. "But we've got different tools now. For the first time, we can see what's happening at the level of molecules and genes." From Keating's perspective, growing a whole arm would be a needlessly complicated parlor trick. But if our regenerative abilities could be sped up even a little, the effect would be extraordinary. "Patients with kidney failure need just 10 percent of their cells back and they can go off dialysis," says Dean Li, Keating's colleague at Utah and now his business partner. "Likewise, when you have a heart attack, there's a big difference between losing 20 percent of your heart cells and 40 percent."

But a chunk of kidney or a piece of your heart is just the beginning. Hydra Biosciences, the company they cofounded in Cambridge, Massachusetts, is also looking at the pancreas, skin, central nervous system, veins, joints, and eyes. For Keating, 48, this last possibility is of more than academic interest. His family has a history of macular degeneration - a condition that degrades the center of the retina - and he's watched at least one relative steadily lose her sight. Should Keating turn out to be right about regeneration, he might find a cure. If he's wrong, he could be squandering a brilliant career in cardiology on a pipe dream.

As an undergraduate at Princeton, Keating ran track. Here in Boston, he often commutes to his Harvard lab on foot, jogging a total of 6 miles to and from work each day. This morning, like most, he ran in the dark, arriving by 5 am despite a forecast for "lethally cold" predawn temperatures. It hardly fazes Keating. In fact, when I called to get directions to the office, he sincerely proposed that I run there.

Keating admits he's daunted by some of his more prominent Harvard colleagues. "At Utah, I was a big fish in a small pond," he says morosely over lunch at a neighborhood deli. The transition was even more difficult because it coincided with his foray into developmental biology. He did, however, enjoy an initial piece of good luck. Shortly after arriving in Cambridge, Keating found that if he suppressed one gene in a zebrafish, the fish lost its ability to regrow fins and organs and instead scarred, just like people. Maybe the gene was easier to switch on and off than anyone thought.

A stray piece of evidence seemed to bolster this theory. Experiments done on sheep in 1991 revealed that fetuses in the first two trimesters will recover from a deep cut seamlessly, but a fetus just a few weeks further along will be scarred for life. "The question isn't whether we still have this program in our genes," Keating says. "The question is, why has this program been turned off?"

More important, can it be turned back on? In Utah, Keating had attempted a rather crude experiment to see if he could get mouse cells to behave more like newt cells. Bruised or cut mammalian tissue reacts by producing scar tissue: tough, fibrous cells that quickly seal off an open wound. Newt tissue, on the other hand, grows a spongy little cap at the site of amputation. Inside that cap, something - perhaps circulating proteins - triggers a genetic program that prompts the endmost cells to reverse their developmental clocks. Like a frog becoming a tadpole, those adult muscle and bone cells "dedifferentiate" back into stem cells - which subsequently divide and proliferate, and finally mature back into whatever kind of tissue the body needs.

It's an elegant system, but the hitch was that no one had been able to get the same thing to happen in mammals. Until the fall of 1998, when, on something of a lark, Keating and his colleagues, postdoc Shannon Odelberg and researcher Chris McGann, decided to treat mouse muscle cells in a petri dish with a liquefied extract made from a newt's regenerating leg cap. Unlike newt cells, mammalian muscle cells change dramatically as they mature, growing fat bundles of ropelike fibers and merging their cytoplasms en masse, like eggs whose whites have run together. Believing that this elaborate structure could be reversed was, researchers thought, like expecting a Ming vase to morph back into a lump of raw clay and powdered pigments.

And yet, under the influence of the newt extract, that was exactly what happened. "Nobody expected it to work," admits Odelberg, still sounding baffled. In a follow-up experiment, the researchers were able to apply growth factors to dedifferentiated cells, making the stem cells mature again to resemble muscle, bone, or fat cells.

It was a staggering discovery. "People had been studying regeneration for years and had zero evidence it

could happen in mammals," Li says. "It wasn't until Mark and Shannon debunked the myth of terminal differentiation that anyone believed this could work."

In light of today's stem cell shortage, Keating's discovery is especially tantalizing. Embryonic stem cells are hard to come by and difficult to work with outside the body. Injecting them into ailing patients invites the same rejection response that plagues organ transplants. The body's own stem cells pose no such problems, but they're in short supply. By contrast, there are plenty of mature cells. Harness those, Keating believes, and we could begin to repair ourselves in situ.

Jump-starting that process has been the problem, but Keating now thinks it might be as simple as delivering a key protein to the damaged area of the body. Ideally, that protein would start a cascade of genetic instructions, which in turn would prompt a cell to dedifferentiate. In fact, Keating notes, cells already dedifferentiate partway when producing scar tissue, so an extra nudge might be all they need to complete the process. Erythropoietin, a standard hormone treatment for leukemia, operates on much the same premise, accelerating the body's production of red blood cells. "My goal," he says, "is to create epo for the heart."

Keating's mouse cell miracle has yet to garner much attention outside the small community of regeneration enthusiasts. This could be because regeneration studies are still not very well respected, but another reason may be that Keating himself is not an especially energetic salesman. Tall and slender with thinning brown hair, he speaks so slowly it's distracting and has a weird tendency to sit with his arm draped over his head. When lecturing, he slides his hands down his thighs repeatedly, as though massaging his quads. Three years in, he remains something of an outsider at Harvard, and he's similarly distant from most of his peers in developmental biology.

Compared with cardiac genetics, developmental biology is poorly understood, and Keating sometimes talks glumly about the burden of being "pathless" - having to forge a new field from scratch. But his isolation may have served him well scientifically. For years, regeneration focused on urodeles - salamanders and newts - which are uniquely hard to study. Among other things, they take two years to mature, don't like to mate in the lab, and can't be cloned or made transgenic. One lifelong salamander researcher has called the animals "our curse."

Keating dropped newts in favor of zebrafish, which can regenerate an amputated fin, a bad eye, severed spinal cord, or even a large chunk of heart. (Keating's current work involves cutting out 20 percent of the heart in different strains of zebrafish and seeing which ones recover.) Unlike newts, however, zebrafish reproduce quickly and are amenable to genetic manipulation. There's even a zebrafish genome project.

Keating is deep in the rather workmanlike task of identifying all the genes involved in heart regeneration, using the zebrafish heart-amputation test. Because each gene codes for a specific protein, Keating hopes he'll be able to use that information to induce regrowth simply by supplying the body with the right proteins at the right time. An infusion after a heart attack, for instance, could slow the scarring process while boosting the production of healthy cardiomyocites.

What remains puzzling, however, is why human regeneration would have been turned off in the first place. Keating's theory is that once we left the swamp and became warm-blooded, our survival priorities changed and scarring became essential, since it kept us from bleeding to death and lowered the chance that we'd develop a fatal infection. "Scarring is the body's duct tape," says Li. Or as Keating puts it, "There was not a huge evolutionary advantage to regrowing your heart if a tiger had eaten half of it."

This is certainly true, but there may be a more fundamental reason our limb restoration program doesn't work anymore: cancer. In order to regenerate, the body has to produce lots of new cells quickly, in a localized area - a process that happens to look a lot like the growth of a tumor. Conceivably, at some point in evolutionary history, it became more important for our body to destroy fast-dividing cells than to preserve them. What this means in terms of restoring our regenerative abilities is harder to determine. Under the circumstances, one might expect animals that regenerate regularly to get cancer more often, but oddly enough the opposite is true: salamanders are one of a very small number of species that don't get cancer at all.

Keating isn't especially worried about cancer, or about any of the slew of possible Hollywood-thriller scenarios (unstoppable cell division! Frankenhearts!) "Cancer is caused by mutated DNA," he says. "And overgrowth diseases are very rare. When we damage our liver, it grows in normal, not twice the size and full of tumors."

For regeneration to work, this would pretty much have to be true, since muscle growth involves a ream of detail that medicine still can't handle - like automatically aligning heart cells so that they contract in tandem. That's not the only obstacle for controlled regeneration, and it's a long walk from zebrafish to people in any case. But the path is no murkier than the one geneticists set out on two decades ago, and the immediate payoff could be greater. The next leap forward in human evolution may be a step closer to the newt.

Contributing editor Jennifer Kahn (jenn_kahn@wiredmag.com) wrote about cancer research in Wired 11.08.

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