In Descartes' day, science communication faced different problems from today: there were no journalists reporting, let alone sensationalizing, science; the Catholic Church did much more damage than any careless commentator could have. Today journalists' skills and their role in communicating science should be recognized as vitally useful, and taken advantage of by scientists. As Heckl noted, "The public would know [almost] nothing about breakthroughs in science if there weren't journalists." Janez Potocnik, the new EC Commissioner for Research from Slovenia, perhaps summed up best the cause and remedy for some of the wounds at the interface of science and society in Europe: "Information for the public is not of secondary importance, something to be tackled when the research is done and results achieved. [It] should be, must be, considered as one of the key elements in any research project." Many would agree that scientists urgently need an image change, but relatively few react to this advice, let alone develop a proactive stance. Heckl is one of the latter, as witnessed by his winning documentary film on nanotechnology, in which he appears on an alpine meadow in checked shirt and lederhosen to explain that he is surrounded by billions of natural nanomachines: "I was the one who said 'let's do something different!' Usually scientists are portrayed as white coats walking around a laboratory with a flask of coloured liquid, now and then peering down a microscope. That separates them from the rest of society."

Descartes certainly did not do much to dispel this popular notion of the scientist. He espoused the need for (his) new ideas and thinking to be communicated to the general public while spending 20 years working as a recluse in Holland, and changing his residence frequently to maintain privacy. The Descartes prizes are an extremely important symbol because they combine the celebration of scientific endeavour with the recognition of science communication. But is Descartes the right choice to lend his name to them, particularly the communication prize? Europe has no shortage of celebrity scientists who might better vie for that honour: Antoine Lavoisier (1743–1794), Descartes' countryman, was a genial and outgoing polymath who interested himself in society and the economy too. Giordano Bruno (1548–1600), an Italian philosopher, travelled the countryside informing the general public that, contrary to what the Church said, the Earth revolves around the sun and not vice versa. He ended up being burnt at the stake for his heroic attempts to communicate science to the people. Alexander von Humboldt (1769–1859), a German naturalist and scientist, travelled to South America and Asia and spent the rest of his life writing and talking about his discoveries and science to ordinary people, as well as to the King of Prussia. With some exceptions, history shows that European scientists around the 'age of enlightenment' not only toiled on their research but also communicated it broadly. It seems as if enlightenment is coming back into fashion.

Andrew Moore

doi:10.1038/sj.embor.7400340

The newt in us

Research on regeneration is a rapidly expanding field and increasingly attracts commercial interest, but therapeutic applications are clearly not around the next corner

The classic area of investigation into the ability of some animals to regenerate lost body parts and injured organs is becoming fashionable again. This promising field in biology and medicine is squeezed between tissue engineering and stem-cell research, but has a much longer history. The study of regenerative phenomena, initiated by eighteenth century pioneers René-Antoine Ferchault de Réaumur, Abraham Trembley and Lazzaro Spallanzani, is considered by many science historians to be responsible for the birth of experimental biology itself. Newts, hydras and planarians are the stars of this 'circus of wonders' and can replace, in an apparently effortless manner, missing or injured tails, limbs, jaws and heads. In some cases, they can even produce whole organisms from tiny fragments. Spurred on by the possibility of a human body that could heal itself, scientists are thus launching a new assault on the genetic and molecular processes that govern regeneration in organisms such as salamanders and flatworms, which have so far kept their secrets.

> Newts, hydras and planarians are the stars of this 'circus of wonders' and can replace, in an apparently effortless manner, missing or injured tails, limbs, jaws and heads

The ability of animals to regenerate is based on the local plasticity of their cells. After injury, progenitor cells migrate to the wound and form a mound called a blastema, in which they multiply and differentiate to replace missing tissue. Although this mechanism is the same in most animals, the origin of the progenitor cells differs significantly. Planarians, for example, rely on a large population of pre-existing totipotent somatic stem cells distributed throughout their body. These so-called neoblasts comprise a startling 20% of the total cells in an adult planarian and can give rise to virtually all cell types. Salamanders prefer to create their own stem cells *ex novo* through the reversal of fully differentiated cells near the wound to an unspecialized, progenitor state. After 'dedifferentiation', these amorphous cells proliferate and differentiate again to rebuild cartilage, bone, muscle and blood vessels as needed. "Urodele amphibians [such as newts] are the champions at regeneration among adult vertebrates," said Jeremy Brockes of University College London, UK. "Urodele regeneration depends on a mechanism for coupling the acute events of tissue injury or removal to the activation of plasticity in differentiated cells." It is harnessing this combination of dedifferentiation and stem-cell biology that might lead to the regeneration of human tissues and organs.

One of the main factors that has hampered regenerative research is the lack of appropriate animal models. Traditional animal systems, such as fruitflies and nematodes, have only limited regenerative capacities, probably because they tend to invest more energy into the production of offspring at the expense of tissue maintenance. Regenerators, by contrast, live longer, require strict control of tissue homeostasis for their survival and are not amenable to genetic manipulation, which makes their experimental use more difficult. To overcome this hurdle, researchers now follow two distinct strategies. The first approach is to unleash the sophisticated tools of molecular biology and genomics on typical regenerators. Planarians seem to be the best candidates, and the US National Human Genome Research Institute (Bethesda, MD, USA) is supporting genome sequencing of the flatworm *Schmidtea mediterranea*. While waiting for the sequence to be completed, researchers can already use several thousand non-redundant cDNAs, together with computational analyses and expression data, in the *Schmidtea* Database (SmedDb, http://planaria.neuro.utah.edu; Sánchez Alvarado *et al*, 2002). With the planarian genome available, scientists such as Alejandro Sánchez Alvarado at the University of Utah School of Medicine (Salt Lake City, UT, USA) and Phillip Newmark from the University of Illinois at Urbana-Champaign (IL, USA) will have information from gene identification and microarray experiments, comparative genomics, RNA interference (RNAi) screens, genetic screens and the identification of promoter sequences, to establish flatworms as the model of choice for studying developmental and regeneration plasticity. Sánchez Alvarado and Newmark have already shown that ingestion of bacterially expressed double-stranded RNA can inhibit gene expression in planarians, making large RNAi screens possible and the discovery of key regeneration genes considerably easier (Newmark *et al*, 2003). "In the not-too-distant future, it will be possible to compare the gene expression programs deployed during the process of regeneration in…many classic models…ranging from planarians and Hydra to axolotls," said Newmark. "Such analyses may shed light on the evolutionary origins of regenerative abilities."

The second strategy focuses on existing model organisms, although not classic in regeneration research, for which a wide array of molecular and genetic tools is available. Because of its ability to regenerate spinal cord, retina and fins, the zebrafish could become one of these new models for studying regeneration. Further support for this organism has come from Mark Keating and colleagues at Harvard Medical School (Boston, MA, USA), who showed that zebrafish can regenerate heart muscle after severe injury (Poss *et al*, 2002). "We demonstrated that zebrafish hearts regenerate through cardiomyocyte proliferation. We also showed that inhibiting cardiomyocyte proliferation abrogated cardiac regeneration and led to scar formation, suggesting there is a competition between the processes of fibrosis and regeneration," said Keating. Zebrafish can restore the ventricular myocardial wall without scarring, whereas in humans damaged myocardium is replaced by fibrotic scar tissue, which impairs the heart's ability to pump and leads to life-threatening arrhythmias.

> It is harnessing [a] combination of dedifferentiation and stem-cell biology that might lead to the regeneration of human tissues and organs

"Our goals are to determine the molecular mechanisms of cardiac regeneration in organisms that have robust regenerative capabilities using genetics, and define the processes that limit regeneration in mammals," said Keating. "Our long-term goal is to regenerate human heart." While Keating feeds his fish, other scientists are looking for alternatives: deer antlers, the only mammalian appendages able to regenerate annually (Price & Allen, 2004); MRL mice, unexpectedly found to be able to re-grow cartilage, skin, hair follicles and even myocardium with great fidelity and no scarring (Heber-Katz *et al*, 2004); and *Xenopus* (Slack *et al*, 2004) are also well-established experimental systems.

The search for the molecular basis of dedifferentiation and cellular plasticity has also made progress with the identification of a small but growing set of genes and biochemical pathways, including Msx1, BMP4, Notch1 and, more recently, the histidine kinase dhkA. In a reverse approach, Sheng Ding and Peter Schultz at the Scripps Research Institute (La Jolla, CA, USA) are trying to design synthetic molecules that induce fully specialized somatic cells to dedifferentiate. Their idea is to build an arsenal of compounds that might reverse human lineage-committed cells to multipotent progenitor cells. These could eventually be reprogrammed to repair damaged or worn-out tissue, which would solve the problem of allogenic rejection and overcome the ethical concerns associated with the use of embryonic stem cells.

> The commercial lure of regenerative biology is also attracting public investors

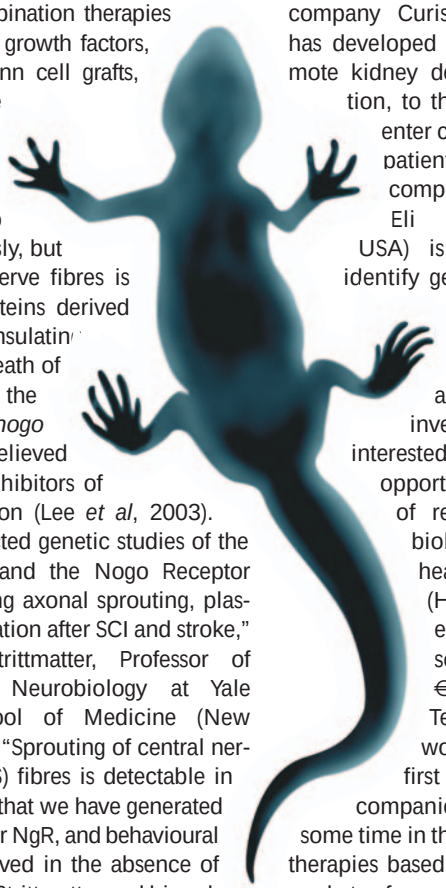
"Ultimately, I believe that small molecules that can control the fate of endogenous progenitor cells represent the future of regenerative medicine," said Ding. "Almost every tissue within our body has reserve endogenous 'stem cells'," he added. "If we know how to control their fate using small molecules, it is conceivable that [they] can be developed into therapeutics for stimulating the body's own regeneration, just like newts." By using an *ad hoc*-generated library of some 100,000 discrete molecules, Ding and Schultz have already identified several compounds that could lead to drugs that regulate the production and fate of stem cells, including the substituted purines myoseverin and reversin (Ding & Schultz, 2004).

Recovery after spinal cord injury (SCI) is perhaps the most highly awaited application of regenerative medicine. SCI affects tens of thousands of patients each year, condemning them to life-long disability. The fate of quadriplegic actor Christopher Reeve, who died last October, has evoked widespread interest in new therapeutic approaches, including stem-cell-based therapies. Several laboratories have announced the reversal of SCI and regrowth of damaged nerves in animal models, which has fuelled hopes for new treatments. Unfortunately, many of these results were not reproducible, igniting a dispute about the tendency of some scientists to "put an over-optimistic spin on their results" (Pearson, 2003).

However, "our understanding of regeneration in the spinal cord has progressed

considerably in recent times, and the long-held view that this system is inherently incapable of repair no longer holds true," commented Gareth Jones and Kerry Galvin at the University of Otago (Dunedin, New Zealand). But clinical applications are still some way away. "There are formidable challenges to be overcome before basic science research can be successfully translated into therapies that will be of benefit to patients. […] In the interim, it is vital for the well-being of patients that scientists, clinicians and also the media learn to be more realistic in their predictions of a complete cure for spinal cord injury," they warned. Nevertheless, they said, some promising approaches seem more clinically feasible than others. These include olfactory ensheathing cell (OEC) grafts (Li *et al*, 2003), combination therapies with 'cocktails' of growth factors, OECs and Schwann cell grafts, and targeting the *nogo* gene.

After SCI, mammalian neurons begin to grow spontaneously, but regeneration of nerve fibres is prevented by proteins derived from myelin, the insulating and protecting sheath of nerves, including the products of the *nogo* gene, which are believed to be the main inhibitors of axonal regeneration (Lee *et al*, 2003). "We have conducted genetic studies of the role of Nogo-A and the Nogo Receptor [NgR] in regulating axonal sprouting, plasticity and regeneration after SCI and stroke," said Stephen Strittmatter, Professor of Neurology and Neurobiology at Yale University's School of Medicine (New Haven, CT, USA). "Sprouting of central nervous system (CNS) fibres is detectable in the mouse strains that we have generated that lack Nogo-A or NgR, and behavioural recovery is improved in the absence of Nogo-A or NgR." Strittmatter and his colleagues are now developing methods to block the NgR pathway as possible therapeutics for the treatment of CNS injury. "These studies provide a strong preclinical basis for initiating clinical studies of NgR antagonists to promote recovery from SCI and stroke," said Strittmatter. "While the Nogo/NgR pathway is not the only limitation on CNS axonal growth, it appears to play a significant role *in vivo*."



Scientists are not the only ones looking at regeneration; businesses are also taking an interest. One of the main players is Hydra Biosciences, a biopharmaceutical company based in Cambridge, MA, USA. Hydra, of which Keating is a co-founder, is developing molecular regeneration medicines, such as proteins and smaller molecules to control cell dedifferentiation and redifferentiation, to offer "an alternative to cell-based therapies for organ and tissue restoration and to currently available therapies for cardiovascular and other conditions." The potential commercial applications of such regeneration drugs are huge, and the company plans to tackle diseases of the heart, vasculature, retina, CNS, pancreas, skin and joints. Meanwhile, biotech company Curis (Cambridge, MA, USA) has developed a protein believed to promote kidney development and regeneration, to the point that it could soon enter clinical trials to treat dialysis patients. Larger pharmaceutical companies are also interested; Eli Lilly (Indianapolis, IN, USA) is supporting research to identify genes that control regeneration in amphibians.

The commercial lure of regenerative biology is also attracting public investors. "We are strongly interested in any kind of investment opportunity within the field of regenerative medicine and biology," said Christof Antz, head of EMBL Ventures (Heidelberg, Germany), an early-stage investor in life sciences technologies with a €26 million fund, the EMBL Technology Fund (ETF). "ETF would like to be among the first to seed novel regenerative companies. If it were possible, at some time in the future, to establish *in vivo* therapies based on cells and molecules, a market of several hundred billion Euro could be realized." In 2004, ETF invested in Ars Arthro AG (Esslingen, Germany), a company that develops implants for the repair of cartilage and ligaments to restore joint mobility. More recently, ETF has started two projects in the field of sensory nerve regeneration in the inner ear and retina.

Regeneration research is expanding rapidly in many directions, and it is difficult to identify all the promising trends.

> … although the future of science is unforeseeable, it is highly improbable that human amputees will see their lost limbs resprout one day

The future of regenerative medicine, however, depends ultimately on whether research will be able to answer central questions such as: why some animals regenerate and others do not, and whether regenerative pathways in humans are irremediably lost and must be engineered from scratch, or if they can be reawakened from a dormant state, and how this can be accomplished. However, although the future of science is unforeseeable, it is highly improbable that human amputees will see their lost limbs resprout one day. More realistically, albeit on a smaller scale, regeneration will flank stem cells, tissue engineering and xenotransplantation in tomorrow's therapeutic arsenal to renovate broken bodies.

REFERENCES

Ding S, Schultz PG (2004) A role for chemistry in stem cell biology. *Nat Biotechnol* **22:** 1–8

Heber-Katz E, Leferovich J, Bedelbaeva K, Gourevitch D, Clark L (2004) The scarless heart and the MRL mouse. *Phil Trans R Soc Lond B Biol Sci* **359:** 785–793

Lee DH, Strittmatter SM, Sah DW (2003) Targeting the NOGO receptor to treat central nervous system injuries. *Nat Rev Drug Discov* **2:** 872–878

Li Y, Decherchi P, Raisman G (2003) Transplantation of olfactory ensheathing cells into spinal cord lesions restores breathing and climbing. *J Neurosci* **23:** 727–731

Newmark PA, Reddien PW, Cebria F, Sánchez Alvarado A (2003) Ingestion of bacterially expressed double-stranded RNA inhibits gene expression in planarians. *Proc Natl Acad Sci USA* **100:** 11861–11865

Pearson H (2003) In search of a miracle. *Nature* **423:** 112–113

Poss KD, Wilson LG, Keating MT (2002) Heart regeneration in zebrafish. *Science* **298:** 2188–2190

Price J, Allen S (2004) Exploring the mechanisms regulating regeneration of deer antlers. *Phil Trans R Soc Lond B Biol Sci* **359:** 809–822

Sánchez Alvarado A, Newmark PA, Robb SM, Juste R (2002) The *Schmidtea mediterranea* database as a molecular resource for studying platyhelminthes, stem cells and regeneration. *Development* **129:** 5659–5665

Slack JMW, Beck CW, Gargioli C, Christen B (2004) Cellular and molecular mechanisms of regeneration in *Xenopus*. *Phil Trans R Soc Lond B Biol Sci* **359:** 745–751

Andrea Rinaldi

doi:10.1038/sj.embor.7400343