From mice to medicine: harnessing the power of regeneration

Professor Malcolm Maden, of the University of Florida, is an expert in the science of tissue regeneration. He and his lab are exploring the molecules and mechanisms underlying the regrowth of limbs and organs in a pair of remarkable animals. In future, their findings could be used to heal a wide range of human injuries.

It is the stuff of science fiction: cut off one of your enemy’s limbs and, hideously, it grows right back. While it may not be quite as instantaneous as we see in the movies – in fact it may take a month or two – one amazing amphibian can do just that. The axolotl is able to regenerate an entire limb, including all of its functional parts – bones, cartilage, joints, muscles, nerves, blood vessels and skin – in full working order. Not only that, but a remarkable mammal, the African spiny mouse, can even grow back large sections of tissue without any scarring. The implications of such abilities for medical science are therefore far from hideous.

These two humble animals are the basis of research in Professor Maden’s lab. His team are working to understand the signalling pathways and processes underlying successful regeneration in both the axolotl and spiny mouse, with the aim of stimulating these pathways to promote similar healing processes in patients. Applications of their research could range from scar-free skin reconstruction in burns victims, to repairing the heart after a heart attack or the lungs following chronic lung disease.

Since the 1940s it has been thought that nerves in the remaining part of an amputated limb produce a chemical signal which stimulates cells beneath the surface of the wound to multiply, forming a mass of cells known as a ‘blastema’. However, it was not until last year that one of Professor Maden’s colleagues, James Monaghan, of Boston’s Northeastern University, identified a potential candidate for the mystery signalling molecule, ‘neuregulin-1’.

Professor Maden’s lab are now working – in a project funded by the US National Science Foundation – to determine the role of neuregulin-1 and other candidate molecules, and to further characterise how cellular signals control the process of limb regeneration in axolotls. Using genetic techniques that explore the impact of deactivating genes in turn, they hope to identify the components of the pathway that causes cells to proliferate, so that ultimately, they can simulate similar pathways in human tissue.

The axolotl is a type of salamander, found only in a small part of Mexico and critically endangered in the wild, but kept alive in labs across the world. Salamanders, like all amphibians, start life as an aquatic tadpole and metamorphose into their adult form. The axolotl, however, is unique in that it remains at the larval stage throughout its life. Research has shown that axolotls, other salamanders, and the closely-related newts can regenerate damaged tissue in organs as diverse as the brain, spinal cord, retina, lungs, skin, limbs, intestines and nerves. Professor Maden’s research focuses on how signalling molecules in axolotls are able to tell when and how much of a limb has been amputated, and stimulate precise regrowth of the missing portion.

The spiny mouse is able to regenerate perfect new skin, including hairs, sweat glands and different muscle layers.

The team are also investigating the intriguing question of how the axolotl’s body knows how much of a limb it has lost and therefore how much to regenerate. Back in the 1980s, Professor Maden found that applying retinoic acid, a derivative of vitamin A, interferes with this process. He therefore hypothesised that retinoic acid forms part of the signalling pathway controlling regeneration. An axolotl that is missing a hand will normally regenerate just a hand; however, if the stump is treated with retinoic acid, an entire limb will regrow in place of the missing hand! Similarly, in frog
After amputating the limb there are several crucial early events.
1. Rapid wound healing and formation of the amputation plane
2. A blastema forms by dedifferentiation of cells at the amputation plane. These cells proliferate and functionally re differentiate into mesodermal tissues again and replace exactly what was cut off in the original amputation.
3. Nerves are required for proliferation of the blastema cells.
Top: Control – amputate the middle of a tadpole tail and it grows back exactly.
Below: add retinoic acid and, instead of regenerating the tail, a whole group of hindlimbs grow.

Axolots are an incredibly unique animal in so many ways. Do you think its ability to regenerate is somehow linked to the fact that it retains its juvenile form into adulthood?

No, the ability of the axolotl to regenerate many organs is not related to its retention of its juvenile form for two reasons: 1) adult newts can regenerate as many organs as axolotls and they have metamorphosed into adults; 2) you can intentionally metamorphose axolotls by giving them thyroid powder and we showed that after metamorphosis they still regenerate as effectively as before metamorphosis. Once a regenerator always a regenerator!

How did you discover that retinoic acid has such significant effects upon regeneration?

The effects of vitamin A were first described by an Indian researcher, I. A. Niazi, in 1978 using frog tadpoles. He was interested in trying to delay metamorphosis to see if that would promote limb regeneration (frogs lose the ability to regenerate their limbs after metamorphosis). He produced bizarre looking extra limbs which were not well analysed and I looked at concentration effects, used different pure retinoids including retinoic acid to establish potency and analysed the structures in detail to show that increasing concentrations of retinoic acid could gradually change the pattern of the limb to be more proximal (towards the shoulder) direction.

Why do you think the signalling pathways involved in regeneration are so similar in such evolutionarily distinct animals as the axolotl and spiny mouse?

Because to regenerate structures such as a limb, evolution is unlikely to have evolved a completely new set of signalling molecules. Instead it is more economical to use the signalling molecules that were used in the first place during development. Because all limbs from fish to mammals develop in essentially the same way then they are going to regenerate in essentially the same way as they will re-use their developmental pathways to regenerate. What needs to be discovered is the differences in the initial response to damage/amputation between a regenerator and a non-regenerator as I think the secret to regeneration lies here – how to kick start the process. The spiny mouse and axolotl can do this kick starting and the normal lab mouse and humans cannot.

Do you find your research is controversial? Have you had interactions with animal rights activists, for example? How do you manage that?

No, I have not had any interactions, good or bad, with animal rights activists. Axolotls have a reputation as being cute as you can see from the large number of websites, You Tube videos and people are so amazed that they can regenerate their limbs that it does not seem to arouse hostile emotions. I also think that being able to regenerate would so obviously be of benefit to humans that most people can immediately see positive value in this research. Of course, axolotls are amphibians and very distant from humans which may mean that they do not arouse such emotional feelings as cats or dogs.

What steps need to be taken before your research can start to be applied to human treatments?

We need to find and identify the kick start molecules (see Q3) which get spiny mice regenerating and are absent in the lab mouse so that we can administer them to the lab mouse and get them regenerating too. Then we’ll begin a programme of applying this molecular knowledge and identified compounds to humans.