The Possibilities of Neurological Regeneration:
An Interview with Dr. Zupanc

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Many areas of medicine have advanced to incredible levels, yet the nervous system remains almost untouchable by treatment. Patients affected by brain and spinal cord injury or neurodegenerative disease have little hope of fully regaining their faculties: These are devastating lifelong conditions. But imagine if a quadriplegic man could heal so effectively that it was as if his spinal cord had never been severed. What if eight weeks after injury, he

could walk, talk, and play sports again? It sounds ridiculous. It sounds impossible. It is impossible – in mammals. However, there is a type of animal that can accomplish this feat: the fish.

Dr. Günther Zupanc of the Northeastern University Department of Biology studies the regenerative abilities of fish in hopes of identifying factors that may be applicable to the development of medical treatments. NU Science had the opportunity to sit down with Zupanc to discuss his career in science, which has led to important discoveries in the field of adult neurogenesis.

Zupanc has been a part of adult neurogenesis research in fish since the founding of the field and his own career as a researcher. When he was still a graduate student, he began experiments imaging brain tissue from adult fish.

"I was very lucky that I had an advisor that allowed me to do many experiments he probably wasn't even aware of," said Zupanc. "So in addition to my thesis, I played with markers that allowed me to identify cells that were dividing."

The results were astounding: the tissue contained unprecedented numbers of dividing nerve cells. Zupanc described his surprise. "We thought 'that's an artifact,' but it was very consistent. It really turned out there's an enormous number of new cells produced in the fish brain." Experiments confirmed that fish possess ten to 100 times the number of new neurons produced in the mammalian brain.

Continued research has revealed crucial differences between fish and humans in their initial responses to injury. Injured neurons in fish undergo apoptosis, which eliminates the damaged tissue with limited inflammation. In mammals, necrotic cell death dominates at sites of injury, which results in a massive release of cytotoxic chemicals. Fish also efficiently recruit immune cells that remove potentially harmful cellular debris from sites of injury.

One of Zupanc's studies identified 24 potential proteins involved in fish adult neurogenesis. This information has enormous potential, because the same or similar proteins may be responsible for the limited neurogenesis present in mammals and could be a target for therapy.

Zupanc also found that fish retain radial glial cells in adulthood, while in most vertebrates they are present only in early development. These cells may create a chemical environment favorable for neuron growth and could also function as structural support for migrating young neurons. They may even be the precursor cells of new neurons.

These discoveries are exciting, but they do not answer a fundamental question vital to understanding the field: Why is it that fish have gained an effective system for nerve generation in adulthood through evolution, but mammals have not?

The "matching hypothesis" suggests that adult neurogenesis was present in all early vertebrates to maintain ratios of central nervous system cells to peripheral cells. When mammals diverged from other vertebrates, muscle growth shifted from hyperplasia (producing more muscle cells) to hypertrophy (enlarging existing muscle cells). Decreased production of peripheral cells meant that developing new neurons was no longer advantageous and resulted in diminished regenerative capacity of the nervous system.

It seems counterintuitive that nerve regeneration was expendable since it would be invaluable as a treatment today. But in early mammals, the inability to regenerate damaged nerve tissue would impose no additional disadvantage because serious nerve damage was rapidly fatal without the availability of prompt medical treatment. Additionally, neurodegenerative diseases, such as Alzheimer's, have an onset so late in development that it could not have been selected against during the short lifespan of early vertebrates.

Despite the progress made in the field, there is more work to be done. One obstacle is biomedical research companies' hesitation to fund labs using a comparative approach rather than the traditional method of exclusively studying mammals. Zupanc recalls the community's skeptical reception to his early research.

"There were only a dozen or so labs in the world, and we were largely ignored. People thought we were exotic people working on an exotic topic," he said. "If they had the same funding and manpower, I would expect major breakthroughs in this area."

Luckily for Northeastern students, Zupanc's passions lie not only in neurobiology, but also in education. Among his major inspirations, he includes his eighth grade science teacher who had a unique approach to education.

"He set up aquaria, brought animals to the classroom, and that was very exciting," said Zupanc. "That showed that biology was much more than learning pages 70 to 75 in a textbook."

Zupanc contributed to the development of a university with innovative curriculum strategies. In this project, initiated by astrophysicist Reimar Lüst, a diverse group of founders aimed to combine the benefits of European and American educational systems.

"On retreats, we sat together and said okay, people with different experience from different backgrounds, let's get together and assemble the perfect ideal curriculum." The result of the project, Jacobs University Bremen, is among the top biology programs in Central Europe. It is clear that just as Zupanc's scientific insight benefits adult neurogenesis research, his passion for education benefits the Northeastern community and students everywhere. ■