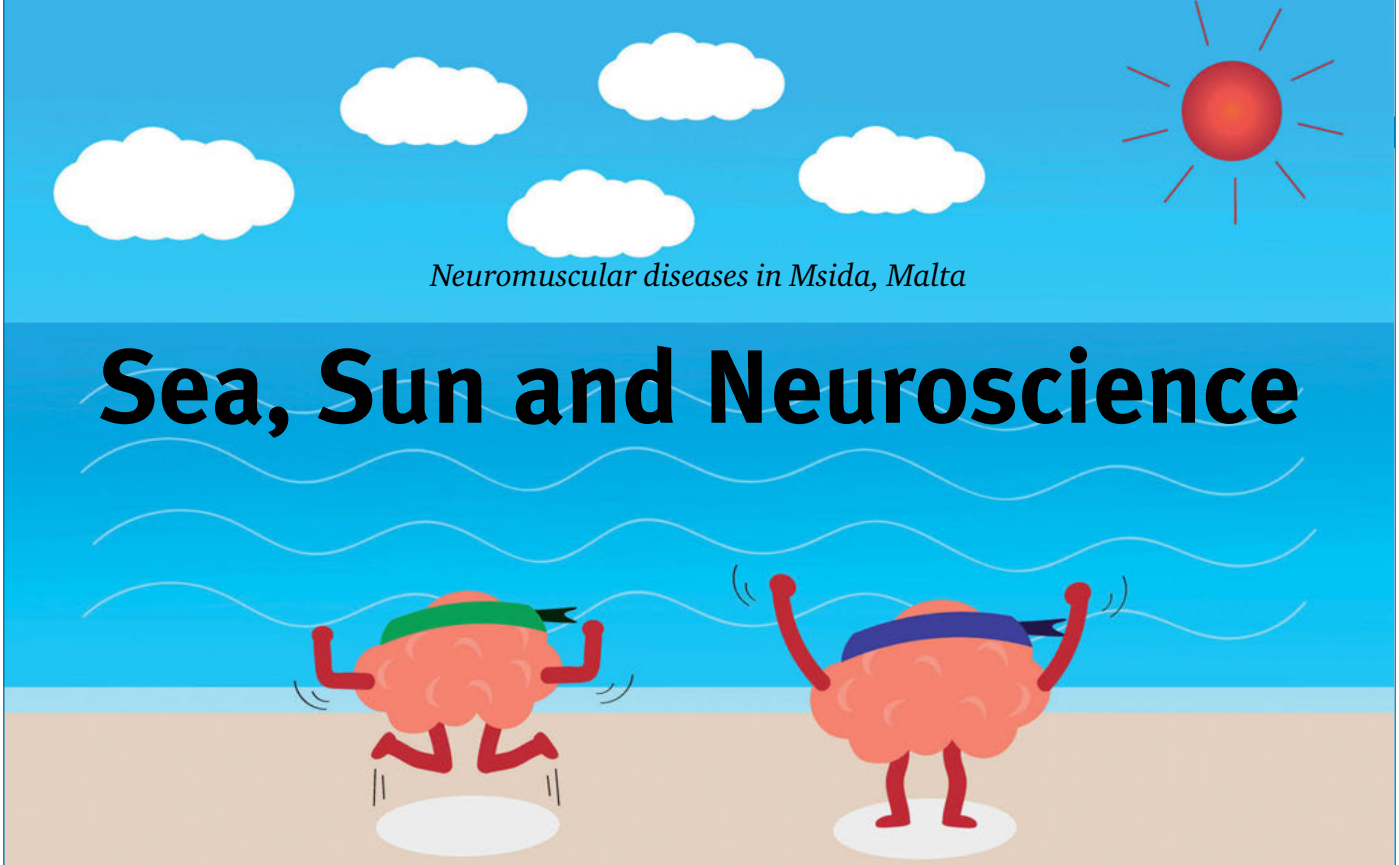
Neuromuscular diseases in Msida, Malta

Sea, Sun and Neuroscience



Spinal Muscular Atrophy is a hereditary, deadly neuromuscular disorder, which affects children. *Drosophila* expert, Ruben Cauchi, and colleagues offer further evidence that the underlying cause of the disease might be a defect in the assembly of the splicing machinery.

Fotolia/jennythip

Affecting between one in six thousand to one in ten thousand live births, Spinal Muscular Atrophy is among the rare diseases. The autosomal recessive disease is characterised by motor neuron degeneration in the anterior horn of the spinal cord, muscle weakness and paralysis. On the molecular level, patients have reduced levels of Survival Motor Neuron (SMN) protein complexes, a condition leading to defects in the biogenesis of small nuclear ribonucleoproteins (snRNPs) and, subsequently, in spliceosome assembly and pre-mRNA processing. It is assumed that SMN is required for the proper development and maintenance of the integrity of the motor unit, the ensemble of motor neuron and muscle fibres it innervates. Whether faulty splicing, which occurs in all cells of the body, could selectively affect neuronal and muscle cells, has, until now, been a matter of scientific debate.

Maltese-French interaction

SMN forms a large macromolecular complex with proteins called Gemins, which might also play a role in the transport of mRNAs within axons. Through studies with genetically-modified fruit flies and yeast two-hybrid assays, Ruben Cauchi at the University of Malta, together with colleagues from France, discovered a functional as well as physical interaction between Gemin 3 and either the enzyme trimethylguanosine synthase 1 (Tgs1) or the assembly chaperone pICln. These two factors were not only involved in the biogenesis of snRNPs (pronounced snurps) but they also influenced the ability of *Drosophila* to fly.

To rate the flight performance of the tiny insects, the scientists took advantage of the Droso Drome, a one-litre glass bottle, coated with an alcohol-based sticky fluid. When they pushed healthy flies into the bottle, they kept flying and eventually stuck to its upper sectors. In contrast, flies, in which Tgs1 or pICln were knocked down or overexpressed, had no power to fly and fell to the bottom of the bottle. Moreover, knock down or overexpression of Tgs1 and pICln resulted in impaired viability in *Drosophila* and revealed that Tgs1 was essential in the muscles and neurons of flies, whereas pICln played an important role in muscles. In yeast, overexpression of either of these two factors resulted in growth defects and the snRNP assembly pathway came to a halt. The observed phenotypes were remarkably similar to those described for the loss of SMN or Gemins. The results, which further strengthen the link between SMA and splicing defects in the neuromuscular system, have recently been published in the journal *Neurobiology of Disease*, (94: 245–58).

In love with flies

Senior author Ruben Cauchi is studying neuromuscular diseases such as SMA and Amyotrophic Lateral Sclerosis (ALS) in *Drosophila* because it is a well-characterised model organism, genetically similar to humans. A plethora of genetic tools are available and it is relatively easy to determine whether loss of a protein function is interfering with, for instance, the acrobatic abilities of the flies. However, the model has its limitations. The SMN-Gemins complex of fruit flies has fewer components compared to the corresponding complex in humans. “We must learn to walk before we can run. So, understanding a simple system first will one day allow us to comprehend a much more elaborate situation in humans,” Cauchi explained. The neurobiologist is a Senior Lecturer within the Department of Physiology & Biochemistry of the University of Malta, where he recently moved with his lab into the newly established Centre for Molecular Medicine and Biobanking.

Formative years in the UK

After graduating from the University of Malta in 2004, Cauchi gained some experience in the UK. He finished his Master’s degree at Imperial College London in 2005 and obtained his PhD from the University of Oxford in 2008. Cauchi said that Oxford prepared him for the challenging life as a scientist and left a lasting impression on him. It was there that he learnt to manipulate flies, or ‘fly pushing’ as he calls it. During his doctoral studies, he was supervised by Ji-Long Liu, now a Professor at ShanghaiTech, and by Dame Kay Davies, the Director of the MRC Functional Genomics Unit at Oxford and an expert in Duchenne muscular dystrophy and Spinal Mus-

cular Atrophy. The neurobiologist admires Liu's scientific enthusiasm and work ethic as well as Davies' fruitful collaboration with patient associations and her entrepreneurial spirit. "In Oxford, I was given the freedom to answer *my* questions," the scientist remembers. "This is easier said than done, since it entails having a sound knowledge of your research theme's context. Nonetheless, it steers young scientists towards independence from day one. Now, I strive to help my own students to take ownership of their projects," he added. After his doctorate, Cauchi did one year of postdoctoral studies at the MRC Laboratory of Molecular Biology at the University of Cambridge, UK, where he investigated RNA processing. For now, he plans to stay at the University of Malta and to focus on genetic research.

Mediterranean neuroscience

Since Malta has been a Member of the European Union (2004), any resident academic can apply for EU-funded projects. Moreover, there are no restrictions for incoming or outgoing EU researchers. "The University offers a competitive salary and bonuses can come through EU grants. There are also national funding schemes but, unfortunately, in recent years these have been geared towards research that is close to commercialisation, a trend also seen in continental Europe," the lab head observed. New members of his lab usually have to pass a short probationary period before being considered for longer projects. "During these weeks, I assess their aptitude for research and their ability to be team members and to observe lab rules. I usually work well with group members who respect the supervision they receive and care about our common lab environment," Cauchi said. Currently, three graduate students and one PhD student are working in his lab.

To do research on an island poses some logistical challenges. "Materials including consumables, DNA or organisms have to be transported from mainland Europe to the Mediterranean via commercial flights, so there can be some delays and a higher price to pay," he said. The lab head also advocates increased funding for technicians for the day-to-day maintenance of labs and animal husbandry. Nonetheless, he considers Malta an attractive place, where science is packaged with sea and sun.

More freedom

"The research base in Malta is still developing and the research environment is not as overcrowded as in other big European countries. Lab heads or principal investigators have more freedom to move into new directions," Cauchi noted. In the coming years, his lab, in collaboration with the ALS Malta Foundation, will collect, sequence and analyse samples of Maltese neuromuscular disease patients with the aim of finding the genetic causes of their disease.

"Malta rivals Iceland in having one of the most homogeneous populations on earth. With so little background noise to filter out, the Maltese genome is simply a treasure trove for geneticists," the scientist explained. He hopes to identify genes, which can serve as targets for next generation medicines for the treatment of the devastating motor neuron diseases.

A special inspiration for his group is Bjorn Formosa, to whom the publication in *Neurobiology of Disease* is dedicated. The former entrepreneur was diagnosed with ALS at the age of 28 and set up the ALS Malta Foundation. "To know that our work can have an impact on patients, drives us to work even harder," Cauchi stressed.

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Photos(2): Cauchi lab/University of Malta

Lab head Ruben Cauchi with two of his students in the flylab (top) and with Bjorn Formosa, founder of the ALS Malta Foundation (left).