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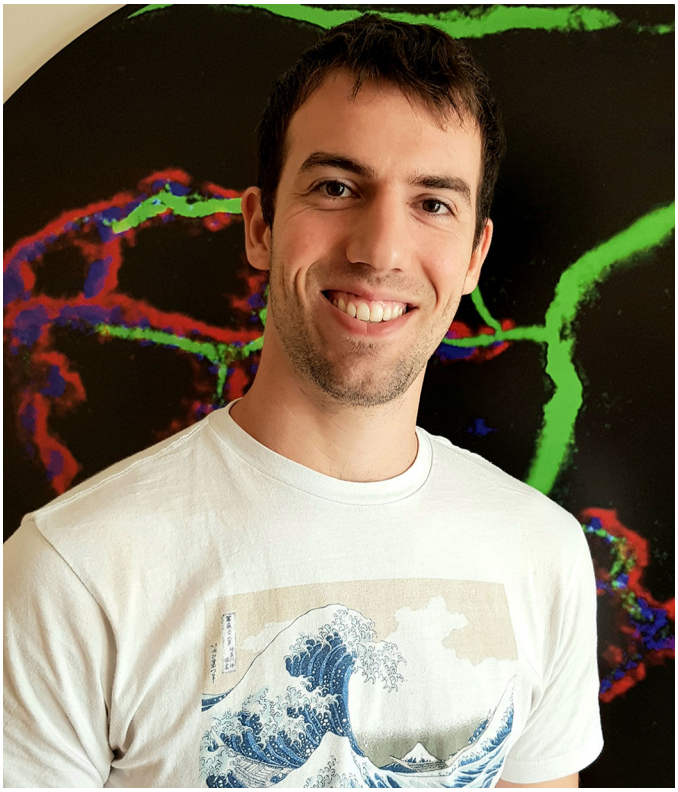
FIRST PERSON

First person – Topaz Altman

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Topaz Altman is first author on 'An *in vitro* compartmental system underlines the contribution of mitochondrial immobility to the ATP supply in the NMJ', published in JCS. Topaz is an MD/PhD student in the lab of Eran Perlson at Tel Aviv University, Israel, investigating basic neurodegenerative mechanisms leading to selective motor neuron death.



Topaz Altman

How would you explain the main findings of your paper in lay terms?

ALS is a fatal motor neuron disease with no treatment available currently. The answer to why motor neurons are specifically sensitive to the degeneration seen in ALS is unknown. In my work, we tried to understand this by finding what is different between motor neurons and other neuronal subtypes. The most vulnerable site in motor neuron diseases is the connection between the skeletal muscle and the motor neuron, which creates a specialized synapse called the neuromuscular junction. By using a simplified lab-on-Chip approach to model the neuromuscular junction, we found that the energy source of the neuromuscular junction is highly dependent on oxidative (mitochondrial) respiration. The mechanism for this is through a relative enrichment of immobile mitochondria in the neuromuscular junction. This finding was compared to what was seen in another type of neuron and muscle connection that is left unharmed in motor neuron diseases, the sympathetic nerves and heart muscle junction. This junction was found to be harnessing fewer mitochondria, and therefore has less dependence on mitochondrial respiration. We believe that this finding will help to guide future studies about the mechanisms leading to motor neuron damage in ALS and other motor neuron diseases.

Were there any specific challenges associated with this project? If so, how did you overcome them?

The project had several challenges. Probably the key challenge was a technological one – how to create and optimize an experimental system that would allow us to study the spatiotemporal role of mitochondria in the synapse. We decided to modify and utilize a compartmental microfluidic chamber we developed recently to model the motor or sympathetic synapses. The hardest part was to adapt this synaptic model system to visualize only the neuronal mitochondria in the neuron–muscle synapses of our microfluidic co-culture system. The main issue was that the muscle is enriched with numerous mitochondria, so a regular staining process with antibodies or mitochondrial dyes did not achieve the desired goal. After many attempts that failed, we came up with the idea of using a lentivirus that encodes a fluorescent mitochondria protein, Tom20. It took a lot of calibration, but by using the microfluidic system that allows the creation of a volume gradient, we infected only the neurons and did not get any muscular mitochondria background, enabling us to efficiently image the pre-synaptic mitochondria in the neuromuscular junction and the sympathetic–cardiomyocyte synapse.

When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

When I did the synaptic ATP measurements using the synaptophysin-fused Ateam 1.03 construct, I was frightened that the result would not meet my primary hypothesis. This was mainly because the FRET imaging protocol did not give any information about the final result while acquiring the data, and a tiresome analysis process was needed. When I got the results of the first experiment, which showed glycolysis inhibition did not further reduce the neuromuscular junction ATP after mitochondria inhibition, it was an amazing feeling; I will not forget it. Luckily for me, the results were replicated and this gave me a strong foundation to build on and to push the project onward.

Why did you choose Journal of Cell Science for your paper?

Journal of Cell Science provides a cutting-edge platform for cell biology research. I enjoy reading papers in this journal and thought it could be a good fit for our story.

Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?

The obvious answer is also the most fitting here. My mentor through the last 5 years was and still is the great head of our research group,

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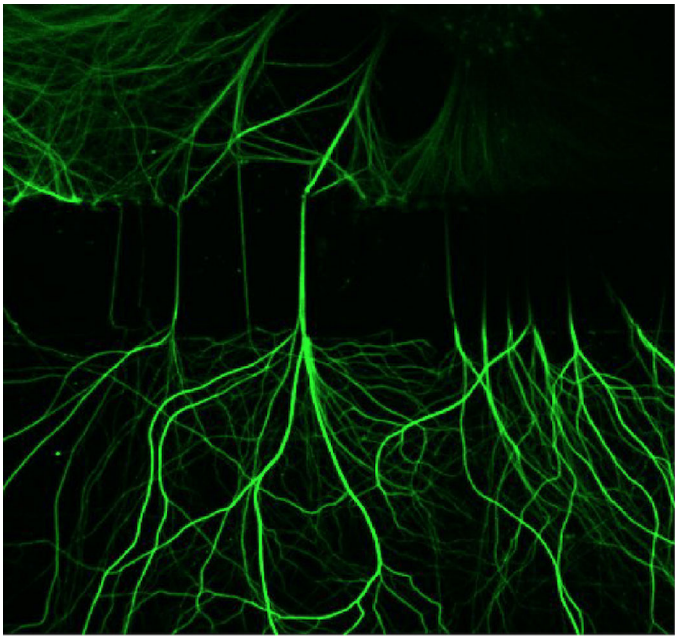

Neurofilament-stained motor neuron axons growing from a ventral spinal cord explant towards the distal compartment of a microfluidic chamber.

Eran Perlson. He kept me going and did not give up on me, or the project – even when times were hard and things did not go as expected. The values of hard work, consistency, innovation and creativity that are much needed as a future scientist were encouraged by Eran all along the way. I think that any young scientist can benefit from having that kind of PI who believes in you and gives you the needed trust but also demands all that is necessary to get the job done.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

I was always a curious kid that refused to let my teachers go home until they gave me all the answers I was seeking. When I went on to medical school, I was astonished by the many subjects that are still unresolved riddles. One of the many questions I faced was what made an ordinary young man, like my 22-year-old friend, go through unexplained paralysis that went on to ALS diagnosis. In medical school, the lesson about ALS explained that there is no known cause or treatment for this horrible disease, and no one could tell me why motor neurons start to die without warning but most patients retain their cognition and sensation. I found out that a lab had recently opened in my medical school that was interested in trying to solve those mysteries, and naturally I was lured there right away to join the team.

“…any young scientist can benefit from having that kind of PI who believes in you…”

Who are your role models in science? Why?

I once attended a lecture by Adrian R. Krainer, the pioneer of alternative splicing and the inventor of Spinraza, the first successful drug to treat a genetic disease, spinal muscular atrophy, with anti-sense oligonucleotides. This huge breakthrough, which will hopefully be acknowledged by a Nobel prize one day, was achieved after 30 years of basic research, unrelated to drug development. Prof. Krainer’s knowledge and basic understanding of the mechanisms leading to changes in splicing of the *SMN* gene led him to this amazing breakthrough. For me, this is the sign that the long road, without shortcuts, is the right way to go in science and to maybe have my breakthrough one day, 30 years from now.

What’s next for you?

First I need to finish my PhD, then onward to finish the MD program. There is still a long road ahead, but if one thing is for certain, it is that I will always keep asking questions and doing basic research to try and answer as many of them as possible.

Tell us something interesting about yourself that wouldn’t be on your CV

Before I started my PhD, I traveled to northern India for two months. Hiking in the Himalayan altitude between the Buddhist monasteries really gave me some of the best ideas I had about life in general and in science in particular. Most of those are still with me today. I’m not sure if it is the walking, the meditation sessions, the spectacular views or the lack of oxygen, but something about that area is a real inspiration. If someone has a crossroad in their life and would like the world’s best atmosphere to get into the right mindset, I would advise them to go there and start climbing.

Reference

Altman, T., Geller, D., Kleeblatt, E., Gradus-Perry, T. and Perlson, E. (2019). An *in vitro* compartmental system underlines the contribution of mitochondrial immobility to the ATP supply in the NMJ. *J. Cell Sci.* **132**, jcs234492. doi:10.1242/jcs.234492