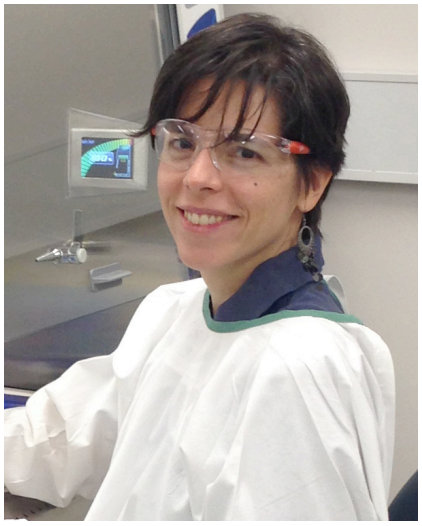
Interview With Dr. Lucia Zacchi, 2015 PMDF Grant Winner



by Mary Ann Chapman, PhD

As a girl, Lucia Zacchi was fascinated by microscopic organisms. She believed that yeast and bacteria had great potential to help solve human problems. Little did she know that her interest in tiny organisms would lead to a research career studying dystonias.

Dystonias are characterized by involuntary, repetitive movements that often result in awkward postures. Only a few treatments are available for dystonias and there is no cure.

Researchers know that alterations in certain genes increase a person's risk of developing dystonia. However, two people may have the same exact genetic alteration and only one may develop dystonia. Dr. Zacchi, a postdoctoral fellow at the Fundacion Instituto Leloir, Argentina and University of Queensland, Australia, is trying to find out why. For her studies, Dr. Zacchi has turned to yeast because they make excellent models for examining the genetic questions that need to be answered in dystonia.

Via e-mail, I asked Dr. Zacchi to tell us a little about her background and research.

1. How did you go from studying microscopic organisms to studying dystonia?

My path toward dystonia was a direct consequence of my goal to use microbes to make a better world. During my doctorate training I learned about the growing list of examples of how baker's yeast had been successfully used to understand human diseases. Yeast is a small, single-celled organism that is cheap and easy to grow, and it is so similar to the cells in our human bodies that we can effectively use it as "model" for human cells. Many of the human diseases that have been modeled in yeast are neurological disorders associated with protein misfolding—when proteins do not achieve their proper functional "shape". Using microbes to understand and find a cure for a neurological disease was a perfect way to realize my goal!

To do this, for my post-doctoral research I joined the lab of Dr. Jeffrey Brodsky, at the University of Pittsburgh, USA. Dr. Brodsky is one of the world's leaders in the study of protein misfolding and associated human diseases. In his lab, I took the challenge to develop a yeast system to find therapeutic targets for early-onset torsion dystonia. Using the yeast system, we were the first to identify potential therapeutic factors for this disease. I am currently working on testing several other potential therapeutic factors we have uncovered and we hope to release this information soon. Our wish is that our findings will lead to a better understanding of how dystonia develops and to a treatment or cure for early-onset torsion dystonia and for other associated diseases.

2. Could you describe your research interests?

Early-onset torsion dystonia is one of the most severe types of dystonia, with an average age of onset of ~13 years and the potential to spread to the whole body. Early-onset torsion dystonia is an inherited disease, and its most commonly associated genetic alteration (mutation) is in the *DYT1/TOR1A* gene. However, inheritance of the *DYT1/TOR1A* mutation does not always lead to disease. In fact, most people with this mutation (~70%) do not develop symptoms. Therefore, other unknown genetic components and environmental factors are required for disease onset. My goals are to identify the unknown genetic components of early-onset torsion dystonia, to uncover the mechanisms that cause disease, and to identify therapeutic targets and biomarkers that will aid in more effective diagnosis and treatment.

3. What are some of the questions we need to answer in the future regarding movement disorders?

One of the fundamental questions that remains unanswered in dystonia is how the disease develops. Disease symptoms are different from person to person and are influenced by different genes and likely by environmental factors. Dystonia researchers have identified a number of genes whose mutations are associated with different forms of dystonia, but it is still largely unclear how any of these mutations leads to disease. Further, we still do not understand what is different in the cells from patients with dystonia compared to healthy individuals, and how these differences lead to disease. This is a critical point and one of our areas of immediate future research. It is also important to know if there are environmental factors associated with disease onset (e.g. stress, smoking, heavy metal poisoning, ultraviolet light exposure, microbial disease). Identifying these factors may help to prevent or delay disease onset.

4. What do you think it is important for patients and/or laypeople to know about research and/or movement disorders?

Throughout my career I have found that there is a general lack of information regarding dystonia both within and outside the academic world. The hard work of foundations like PMDF, Dystonia Medical Research Foundation (DMRF), the Michael J. Fox Foundation, and groups like the Australian Dystonia Support Group, among many others, are helping to spread the word by informing and educating the general public, politicians, and scientists about dystonia and other disorders. I believe public awareness of the diversity and symptoms of movement disorders is very important. Informed people can better understand the needs of those afflicted by movement disorders and can demand that government policies are developed to enhance the quality of life of patients, in addition to securing funding for research.

I believe it is also critical that scientists (like myself) meet with the patients. This interaction has a direct benefit for both parties. On the one hand, I have found that patients are very interested in learning about research advances related to their diseases, even more so if they are supporting the research through their private donations. On the other hand, meeting the patients allows scientists to put a face to the disease. Through the ups and downs in research, remembering who we are doing this for is critical in keeping up the fight.

5. How will the PMDF money help you to pursue your research goals?

Research in the laboratory is costly. At a time when funding from government agencies is tight, grants from foundations like PMDF are fundamental to support projects that are close to the finish line. Indeed, the grant we received from PMDF has been critical in helping us to finish two

related projects in which we are uncovering potential therapeutic factors (genes) for early-onset torsion dystonia. Without the help from PMDF, wrapping up these projects would have been difficult, delaying publication of the results. We are very grateful to PMDF (and also to DMRF) for their trust and support. We hope our efforts will provide novel insights into disease development, identify biomarkers for diagnosis, and uncover medically relevant targets for the design of more effective therapies for dystonia.