THE GEORGE S. WISE FACULTY OF LIFE SCIENCES
DEPARTMENT OF CELL RESEARCH AND IMMUNOLOGY
PROF. ORNA ELROY-STEIN

TEL AVIV UNIVERSITY אוניברסיטת תל אביב

הפקולטה למדעי החיים ע"ש ג'ורג' ס' וייז
המחלקה לחקר התא ולאימונולוגיה
פרופ' אורנה אלרואי-שטיין

December 23, 2018

Orna Elroy-Stein's Lab, Tel Aviv University

Research Update – December 2018

2018 has been a very important year for VWM research in our lab. First, we published our high-impact drug screening project. Excitingly, a clinical trial is planned by a pharma company for 2019 based on our discovery. Second, we have reached a point of significant understanding related to the molecular challenges eIF2B-mutant cells (VWM) have to face, and how they manage to deal with it. It seems that certain cell types perform better than others in compensation approaches. We would like to further understand their molecular strategies in order to be able to develop better drugs. Third, initial characterization of our new VWM mouse model leads us to unexpected, novel, and exciting directions.

In terms of manpower, Melisa Herrero-Bocco, Shir Srour-Mendelbaum, Reut Sharet-Eshed and Mika Rotem continue to work hard and generate important data as part of their PhD studies; Maron Daw happily decided to start his graduate studies in the lab and already managed to successfully perform challenging experiments; and Dr. Andrea Atzmon continues to be the top-best research associate who continually provides scientific and technical assistance to everybody and runs projects related to VWM biology. Moreover, Liya, Dekel, Liat and Niv, four undergraduate students, joined us for part time help and they are just as thrilled as we are about science.

Below is a short summary of our achievements during 2018, combined with our missions for 2019.

Drug screening project

This project was successfully finalized and published in the respected journal 'Frontiers in Molecular Neuroscience' (https://www.frontiersin.org/articles/10.3389/fnmol.2018.00336/full). The bottom-line of this study is the discovery of S1R protein as a potential target for the treatment of VWM patients. Another drug, also known as S1R activator and owned by a specific pharma company, will be used sometime during 2019 for a small clinical trial designed for VWM patients. Before this pharma company publically releases this information, I cannot provide more details. What I can say at this point of time is that I work with them, we are all very excited, and hope for good news.

Our new (additional) mouse model for the study of VWM disease

In my previous scientific report for 2017, I indicated that we were at the final stages of a (long) process of generating an additional mouse model, which harbors a different mutation

in eIF2B-5 gene. During the first half of 2018 we already had a big colony of homozygous mice of this new strain. Reut's project is to characterize their abnormalities. To this end, she currently performs live brain MRI scans for groups of 10 mutant and 10 normal mice, throughout their growth, at one month intervals. Each mouse is scanned multiple times, starting at 3-weeks of age; now they are ~6 months old. We decided to continue the scans for 6 additional months. This highly expensive and complicated project will teach us a lot about disease progression and will give us a high resolution insight about brain development prior to appearance of severe motor symptoms. Reut became an MRI expert, as lately she started to analyze the images all by herself, using algorithms developed by Prof. Yaniv Assaf, our collaborator and head of TAU neuroimaging lab (http://neuroimaging.tau.ac.il/). We are eager to see the final results but we must be patient. Reut also checks mice gait using sophisticated computerized system and then analyzes various parameter of their motor functions. It seems the disease of the new mutant strain is developing slowly under normal conditions, but when Reut applied stress which induces high fever, the increased sensitivity of eIF2B-mutant mice is definitely apparent. This project leads us to think about new directions, related to the response of eIF2B mutants to stressors. Reut plans to start soon to treat the mice with several potential drugs.

Effect of eIF2B mutation on differentiation of oligodendrocytes

During 2018, Melisa managed to complete all the required experiments, so now this project is ready for submission for publication in a scientific journal. The take-home message of the project is the negative effect of eIF2B mutation on the process of differentiation and maturation of brain oligodendrocyte precursor cells (OPC) to mature myelinating oligodendrocytes. This conclusion is in contrast to what was claimed previously by other researchers, who argued that only astrocytes, but not oligodendrocytes, have a cell-autonomous defect. Melisa also showed that the anomaly is linked to impaired ability of OPCs to generate available energy (ATP) in the mitochondria, despite increased abundance of mitochondria as a compensation strategy.

Effect of eIF2B mutation on cellular metabolism of astrocytes and Omics-related big data analysis

Melisa is working now on brain astrocytes. Astrocytes are considered the most sensitive cell type for eIF2B mutation and therefore are heavily involved in the disease. Melisa already discovered a major deficit in astrocytes' cellular metabolism and currently works hard to further dissect the involved molecular pathways. Maron Daw, our new graduate student, joins forces with Melisa and together they synergize towards important discoveries, which are related to compensation strategies undertaken by eIF2B-mutant cells in order to survive. Mika Rotem is also studying this important question, but she looks at it from a different molecular angle. Shir is also part of this big project, from the bioinformatics point of view. Andrea has already generated un-biased datasets using mutant fibroblasts, and Shir plans to generate additional datasets using normal and diseased astrocytes under

various stress conditions. The aim is to look at differences in expression programs due to eIF2B mutation, at the highest molecular resolution possible. Shir will apply state-of-the-art bioinformatics algorithms and tools to gain novel insights about successfully compensated and non-compensated deficiencies, on the transcription and translation levels. It is important for us to combine all insights together in order to have a high-resolution birds-eye view of what is going on within eIF2B-mutant cells. We believe it is important in order to fully understand how to design advanced additional therapeutic modalities in order to help mutant astrocytes overcome their difficulties.

We hope for an exciting and successful 2019!

Thank you for your support and involvement!

We wish you a Happy Holiday and a Wonderful New Year

Prof. Orna Elroy-Stein, PhD

On behalf of Andrea, Maron, Melisa, Mika, Shir, and Reut –
Elroy-Stein's lab VWM research team