End of year report

2015 Project

Rett Syndrome Research Trust

Reactivating the healthy but silent copy of the "Rett" gene

The funds provided to your organisation for the current year by TFWA Care were donated following the approval of the TFWA Management Committee and board. Among the prerequisites for funding by TFWA Care are transparency and accountability. We would be grateful if you could send us a brief summary of the project, the objectives achieved, problems encountered, impact on the local community and indicators of the project's success. We will share the report with the Management Committee at the end of year meeting.

Please do not hesitate to report on the project's successes as well as any aspects that did not go according to plan. This serves to provide a greater understanding of the challenges and issues encountered by the communities on whose behalf your organisation is working. Any quantifiable indicators will also be helpful in your report.

Thank you.

Project details

1. Please summarise in a few words the project supported by TFWA CARE, including the principle objectives and duration.

   TFWA generously supported the Rett Syndrome Research Trust's project called *Reactivating the healthy but silent copy of the "Rett" gene*. The principle objective of the project was to screen thousands of compounds and identify one or more that have the effect of replacing the faulty gene in Rett Syndrome on the active X chromosome with its healthy counterpart on the dormant X chromosome. Compounds that achieve this could lead to cancelling out Rett Syndrome's terrible symptoms in girls and women who suffer with this disease. When this project was launched in 2012 it was conceived as having a three-year timeline that would end this year. But because of exciting potential, we are expanding the screen to a multi-lab consortium that will continue over the next two years.

2. What activities were carried out within the scope of the project over the course of the year?

   Over the year the project continued to screen thousands of compounds that could have the effect of unsilencing the healthy but dormant "Rett" gene. Much of this effort took place at the University of North Carolina Medical School. We are pleased to report that over the past year other labs have joined the effort and are working with RSRT and UNC on this approach, including Harvard Medical School, the Fred Hutchinson Cancer Research Institute, and the University of Massachusetts Medical School.

   These scientists are working in a non-traditional fashion. They are bucking the long-established tradition of keeping data under tight wraps and are sharing their findings with each other to speed treatments. At an in person meeting this past May several labs reported "hits" (compounds that in the lab were able to reactivate the silent but health "Rett" gene). Because these labs are working together and sharing resources, it will make further validation of this result more efficient—each lab is now independently validating, providing unbiased data. Meanwhile, screening of other compounds has continued. These scientists will meet with RSRT in mid-November to share data and progress.

Evaluation

3. Has the project been successful? Please outline the success factors for each objective as well as the challenges encountered and solutions adopted to overcome them.

   Yes, the project has been successful in that it has eliminated thousands of compounds as possibilities for activating the silent but healthy "Rett" gene. Eliminating compounds as possibilities is important because it allows scientists to focus on a narrower and narrower list of potentials. The fact that several labs reported "hits" this year is also very important. Validation of these "hits" continues. Where there is one "hit" others are likely to follow.

   One of the project's challenges has been the speed and efficiency of the compound screening. With multiple labs now involved, the project has become much more efficient and has been able to test many more compounds than we originally thought possible. The project has become a true consortium of scientists. We are proud at RSRT at having played a key role in creating this consortium. Treatments and ultimately a cure for Rett Syndrome are unlikely to come from a single lab working in isolation. It's going to take the collaborative efforts of many scientists working across numerous disciplines and labs. This project has achieved that kind of collaboration.

   It is also important to note that the strategic approach of activating the silent "Rett" gene was put on the map by RSRT. No one was attempting this until we aggressively pushed this approach. The pharmaceutical industry is now interested in this strategy, validating our decision. A few years ago the pharmaceutical industry had very limited interest in Rett Syndrome. Now, partly because of this project and the possibility that a drug could be developed that could have a dramatic effect on Rett symptoms, we have caught the attention of industry. This is a very good thing for moving us closer to what's most important—changing the lives of those suffering with Rett.

4. Did the work accomplished this year help you learn lessons that will benefit future work?

   Absolutely. There are two main reasons we are so eager to continue the screen—1) because there were preliminary "hits" from the screen. We learned from these and they inform the screening of more compounds. 2) Because it has become a true consortium of labs the project is much more effective and efficient than when we launched it. We can screen more compounds in a much faster time than when we launched. This gives us a much greater chance of success over the next two years. We also now have new expertise on the project. For example, Jeannie Lee, professor

of genetics and pathology at Harvard Medical School, is now working with us and will do important work on this approach moving forward. She brings unparalleled expertise in X inactivation.

Sustainability

5. How has the project had a positive impact on the community/ies at the core of the project and what will be the long term benefits? Please explain if the project has helped empower the beneficiaries by providing greater autonomy.

   The community at the core of the project are the 350,000 girls and women around the world afflicted with Rett. Rett strikes little girls without regard to their nationality, race, or socioeconomic status. It is truly random, afflicting approximately 1 in 10,000 births. Rett symptoms are devastating and painful, physically and emotionally. Most girls with Rett cannot walk or talk, and many have symptoms such as seizures, severe scoliosis, repetitive hand motions, breathing difficulties, and problems chewing and swallowing that often lead to the need for a feeding tube. Girls and women with Rett need 24-hour-a-day care. They are a highly vulnerable population. Yet it has also been demonstrated that girls and women with Rett can have normal cognitive function; their minds are active but they are trapped in bodies that are so severely impaired that they cannot express their intelligence, thoughts, hopes, and dreams.

   The long term benefits to this community if this project is successful are difficult to measure at this point. Our great hope is that we identify a compound that has a significant impact on the disease, giving this population greater independence, autonomy, and the ability to be productive, happy citizens. It is also possible that we will identify a compound that does not have as significant an impact as we'd hoped, but instead leads to some improvements in symptoms. Whether we make modest or major changes to symptoms, any gains are important as we must improve the quality of life for these girls and women. We believe that our continued persistence will pay off and continued screening could lead to discovery of compounds that could change the lives of the hundreds of thousands of girls and women suffering with Rett Syndrome. This is why expansion of the project is so important.

6. Will the project continue in the future or is it now complete? Will further funding be required in the future to complete the work? Please indicate if the initial funding request was a multi-year project. ** (see footnote)

TFWA has supported this project annually for three years. We are now expanding the project because of the exciting potential that has been revealed. We are seeking further funding from TFWA Cares to help us do this. Specifically, we will work with Jeannie Lee at Harvard University, a world renowned expert in X inactivation, to continue screening compounds.

Finance

7. Please provide a summarised breakdown of how TFWA Care funds were utilised for the project.

   TFWA's 2015 support helped us pay for the time that the lead scientist at the University of North Carolina and his team devoted to this project. It also supported important equipment such as the robotic device used to test thousands of compounds, and housing and care of mice. The approximately $35,000 (US Dollars) in funds that TFWA contributed last year were used as follows:

Lead scientist (Ben Philpot) time	$5,000
Second scientist (Terry Magnusson) time	$5,000
Equipment and supplies	$11,000
Animal care	$14,000
Total:	$35,000

Please attach your latest annual report as well as any pictures you would like to use to illustrate this report.

We would be grateful if you could send this to John Rimmer (j.rimmer@tfwacom) by **November 6 2015 at the latest**.