IRSF Spotlight: Omar Khwaja, MD, PhD, MCRP of Children's Hospital Boston

By Jim Keller

In 2009 IRSF agreed to fund a Research Clinical trial conducted by Dr. Omar Khwaja and his team at Children's Hospital Boston. The proposal titled "Pharmacological Treatment of Rett Syndrome by Stimulation of Synaptic Maturation with IGF-1," represents the first potential disease-modifying therapy to be tested in RTT patients. This was greeted with an outpouring of enthusiasm from the Rett syndrome community.

Federal regulations require that research which involves human subjects must be substantiated by the approval of an Institutional Review Board (IRB). After extensive review of the safety aspects of this trial, we are pleased to announce that IRB approval has been granted and that Dr. Khwaja's groundbreaking trial is ready to begin.

The study involves investigators testing a drug called Increlex®, to be provided by Tercica, Inc. (a subsidiary of the IPSEN Group). The drug is an engineered form of the human protein Insulin-like Growth Factor-1 (IGF-1), which has been previously approved by the FDA for treatment of a rare condition in children called Laron syndrome. Preliminary evidence has suggested that targeting the IGF-1 signaling axis may provide a potential avenue for therapy in RTT.

To commemorate this occasion we would like to share a few words and highlight the achievements of this well-respected investigator and potential pioneer in the quest for real treatments for Rett syndrome.

Dr. Khwaja completed his undergraduate training at the University of Cambridge where he studied Natural Sciences, specializing in Developmental Biology and Neuroscience. There he learned to manipulate developing mice embryos to understand the connections that develop between embryonic cells fated to become part of the nervous system. As a graduate student at Cambridge he worked on physical and long range mapping of the human sex chromosomes, using molecular genetic techniques to map genes involved in Turner syndrome, another rare disorder. After medical school, Dr. Khwaja trained in pediatrics and newborn medicine at the Royal London Hospital and Great Ormond Street Hospital for Children before moving to Australia and the Royal Children's Hospital and the Murdoch Children's Research Institute (MCRI) where he completed his neonatology training and did a fellowship in Clinical Genetics. At MCRI he met his first patients with Rett syndrome. Later, Dr. Khwaja went on to train in Child Neurology at Harvard and following fellowship training, joined the faculty at Children's Hospital Boston where he focused on neurological diseases of the fetus and newborn as well as children with neurogenetic conditions such as Fragile X and Rett syndromes. There he became Chief Resident and met Dr. Alan Percy of the University of Alabama, Birmingham (UAB), which stimulated his interest in Rett syndrome. In 2007, Dr. Khwaja became the founding Director of the hospital's Rett Syndrome Program. Shortly after he met Professor Mriganka Sur at Massachusetts Institute of Technology (MIT) and learned of his laboratory's work using IGF-1 to treat mouse models of Rett syndrome. In addition, he is site Principal Investigator for the Rett Syndrome Natural History project of the NIH and serves on IRSF's Professional Review Board and SRB.

What prompted you to begin a career in research?
As an undergraduate I became fascinated by the rapidly emerging fields of developmental biology and

neuroscience. As a graduate student I saw directly the power of molecular genetics to probe the basis of disease--particularly those that affected the brain. As a pediatric neurologist we now are at the point where we can use powerful molecular techniques to understand and begin to treat neurodevelopmental disorders at the most fundamental level. I've been fortunate to have a wonderful mentor in Dr. Joseph Volpe who has been not only a role model as a superb and caring physician, but also a deeply scholarly neuroscientist. His vision of translational research, that existed before the phrase was coined, has been an inspiration for me to continue to focus research questions on real life clinical problems that face children with neurological disease. The prospect of being able to treat previously untreatable neurological disease is my main motivation.

What is the single most rewarding aspect of conducting Rett syndrome research?
To work with amazing individuals and their families in a disease where there is such an incredible community of physicians, scientists and advocates and the realistic prospect of reversing symptoms of the disease and treating it at a molecular level.

What is a potential positive outcome of the research you're conducting that is specific to your IRSF Award?
We hope that our research will show improvement in a number of symptoms of RTT, but particularly autonomic and respiratory function as well as motor function.

If you could pick any one symptom of Rett syndrome to prevent or to provide relief for, what would it be?
That's a hard question to answer, as I would like to treat all of them. Perhaps the most pressing would be to adequately treat seizures and improve hand use and communication.

What other diseases does your research focus on?
My other research focuses on understanding how brain development occurs in the fetus using advanced MRI techniques and, especially, malformations and injury to the brain before birth.

What else would you like the RTT community to know about you?
As the father of three young toddlers I don't have much time for hobbies now, but when time and weather permits I love to sail in Narragansett Bay, RI and the waters around Block Island, Buzzards Bay, Martha's Vineyard and Nantucket. In my spare time I read; especially British history and Scandinavian crime fiction. The books of neurology authors such as Oliver Sacks continue to inspire me and I hope one day I'll be able to write as eloquently.I am fortunate to learn from experienced clinicians such as Dr. Percy, Jane Lane (UAB), Dr. Steve Skinner (Greenwood Genetic Center), Dr. Kay Motil and Dr. Jeff Neul (Baylor College of Medicine) and to meet RTT families from across the country. I enjoy the stimulation and intellectual interaction with other researchers both within and outside the RTT field.

**Dr. Khwaja and his team have secured additional funding for this clinical trial through grants provided by Harvard University's Catalyst Pilot Awards for Clinical Translational Research (and Autism Speaks).*