

IRSF Investigator Spotlight: Rajiv R. Ratan, MD, PhD of Winifred Masterson Burke Medical Research Institute, Weill Medical College of Cornell

By Jim Keller

2010 was a landmark year for IRSF as it rolled out its Translational Research Grant Program. The program, consisting of two grant mechanisms that provide funding for early and late stage research initiatives focused on treating and reversing symptoms of Rett syndrome, was highly successful yielding 10 HeART grant Awards and two ANGEL grant Awards. One of the former Award recipients was Dr. Rajiv R. Ratan for his project titled “Novel screening methods for quantitative, homeostatic regulation of MeCP2.” This project

utilizes a screening strategy that aims to identify drugs that modulate MeCP2 stability or synthesis in human cells. Drugs that normalize MeCP2 levels and increase BDNF release from cortical neurons will also be identified. Since it’s crucial that these drugs do not increase MeCP2 levels beyond a normal (homeostatic) range, Dr. Ratan’s strategy involves a carefully controlled method to modulate MeCP2 levels in order to circumvent this potentially tragic outcome—think light from a dimmer switch. The drugs identified will be ready for testing in cell-based and animal models of Rett syndrome. Positive screening hits will also undergo optimization by medicinal chemists, including Dr. Alan P. Kozikowski of the University of Illinois, Chicago, a long standing collaborator. Through this project, Dr. Ratan’s group will seek to restore MeCP2 levels in the nucleus of patients’ nerve cells--this is particularly interesting since research has shown that restoration of MeCP2 levels in afflicted female mice can reverse motor, cognitive and autonomic symptoms.

Following a Residency in Neurology at Johns Hopkins University, Dr. Ratan became interested in the area of genetically programmed cell death (apoptosis). His work examined whether cell death signaling pathways can be induced by pathological stimuli such as oxidative stress. In 1992, his research fostered data that showed that oxidative stress could induce apoptosis, and surprisingly that this involves the active transcription of certain genes in order for the cell to die. Since then Dr. Ratan’s lab has tested antioxidants and their effects on nerve cell death and mechanisms of neuroprotection. His lab’s studies have repeatedly taken them to the nucleus of the cell where the activation of genes is highly regulated--in several neurological conditions gene transcription is dysregulated. Through understanding MeCP2’s role in Rett syndrome they hope to leverage their expertise to help solve the Rett syndrome riddle. While he is not the father of a child with Rett syndrome, Dr. Ratan’s own daughter has inspired a vested, personal interest in him to see individuals worldwide cured of this devastating disease. Dr. Ratan is the Director of the Burke/Cornell Medical Research Institute—a major translational center for neurodegenerative and neurodevelopmental disorders and Professor of Neurology, Neuroscience and Rehab Medicine at Weill Medical College of Cornell University. In addition, he serves on IRSF’s Medical Advisory Board (MAB).

What prompted you to begin a career in research?

I was “bitten by the bug” at a very early age. As an undergraduate at Amherst College, I majored in Neuroscience. It became clear to me very early on that the brain is an important and vastly underexplored frontier. Accordingly, I was able to join the laboratory of Gaylord Ellison at UCLA studying a model of schizophrenia and its neurochemical correlates. I had such a good experience there that I did an honors thesis



my senior year at Amherst, and was fortunate to be accepted to an NIH funded Medical Scientist Training Program.

What is the single most rewarding aspect of conducting Rett syndrome research?

Working together with a very talented and smart team of people to conquer suffering in young girls.

What is a potential positive outcome of the research you're conducting that is specific to your IRSF Award?

We hope that by identifying an enzyme or enzyme(s) that regulates MeCP2 stability via a novel MecP2 screening method, we will develop a drug that will allow one to increase MecP2 within a homeostatic range.

If you could pick any one symptom of Rett syndrome to prevent or to provide relief for, what would it be?

Loss of communication and thinking abilities. Obviously this may be the most challenging, but being able to communicate and think is part of what makes us uniquely human.

What other diseases does your research focus on?

My lab is very interested in brain repair in a host of diseases including stroke, traumatic brain injury, Huntington's disease, Alzheimer's disease and Parkinson's disease. However, I believe that many of the answers to these diseases will come from the successful treatment of children with impairments that reflect many of these primarily adult conditions. Thus, Rett syndrome may teach a great deal about motor and cognitive rehabilitation.

What else would you like the RTT community to know about you?

My research is evaluating the hypothesis that disease is a failure of adaptation. Understanding how neurons adapt to oxidative stress, hypoxia, mitochondrial dysfunction, etc. will provide viable therapeutic targets for treating neurological conditions. I direct a wonderful research Institute in Westchester County affiliated with Cornell, and I have a wonderful wife (who is an obstetrician) and two remarkable children. My family members are avid sports participants and spectators.