

Investigator Spotlight

ARCHIVE

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Monica J. Justice, PhD, Baylor College of Medicine

Yi Eve Sun, PhD, University of California, Los Angeles

Liang Zhang, MD, PhD, University Health Network, Toronto Western Research Institute

John Christodoulou, AM, MB, BS, PhD, FRACP, FFSc, FRCPA, CGHGSA, Children's Hospital at Westmead, Sydney, Australia

Aleksandra Djukic, MD, PhD, Tri-State Rett Syndrome Center, Montefiore Medical Center, Albert Einstein College of Medicine

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Huda Y. Zoghbi, MD, Howard Hughes Medical Institute, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Baylor College of Medicine

Gail Mandel, PhD, Howard Hughes Medical Institute, Vollum Institute, Oregon Health and Science University

Note: The IRSF Spotlight's intent is to give our lay and scientific communities an idea of who Rett syndrome investigators are both as a person and a scientist working to make Research a Reality.

Investigator Spotlight: Alan Percy, MD, The University of Alabama at Birmingham, Civitan International Research Center

With the arrival of fall, IRSF is preparing for October Rett Syndrome Awareness Month (ORSAM) one of our busiest months of the year! With ORSAM in mind, we would like to take the opportunity to highlight a long time prominent figure who has been so dedicated to Rett syndrome. Dr. Alan Percy from the University of Alabama at Birmingham has worked in Rett syndrome research for almost 30 years. Dr. Percy is a pediatric neurologist at UAB, where he currently serves as Professor of Pediatrics, Neurology, Neurobiology, and Genetics. He is the Director of the Rett Clinic and Research

Center, Associate Director of the Civitan International Research Center, and an UAB Intellectual and Developmental Disability Research Center Principal Investigator.

Dr. Percy was one of the first physicians, along with Dr. Vanja Holm and Dr. Mary Coleman, to recognize Rett syndrome in the United States in 1983. He then attended the 1984 Rett syndrome conference in Vienna organized by Dr. Andreas Rett. Since that time, Dr. Percy has actively pursued clinical and basic research studies of Rett syndrome and established Rett clinic centers at Baylor College of Medicine and later at the University of Alabama at Birmingham. He is also the principal investigator of the Rare Disease Clinical Research Consortium on Angelman, Rett, and Prader-Willi syndromes. Since 1983, he has authored more than 120 scientific papers on Rett syndrome and is a co-author of The Rett Syndrome Handbook.

Besides his work in the clinic and the lab, Dr. Percy has occupied prominent leadership positions in numerous academic neurological societies including Past President of the Child Neurology Society and the Child Neurology Foundation and Director of the American Board of Psychiatry and Neurology and is a Fellow in both the American Academy of Pediatrics and American Academy of Neurology. Dr. Percy recently co-chaired the Family Education and Awareness Conference at the 7th World Rett Syndrome Congress hosted by IRSF. Since 2007, he has served on the IRSF Medical Advisory Board.

Dr. Percy is a beloved physician and a highly recognized authority of Rett syndrome and other neurometabolic rare diseases. He has been involved with Rett syndrome since the early days, and in 2009 Dr. Percy received IRSF's highest award for a clinician, "The Art of Caring Award". Thank you for your true dedication, Dr. Percy.

What prompted you to begin a career in research?

I began my career in research based on my undergraduate experiences in biochemistry and my interest in child development and child neurology through my mentors in medical school. I was already well-entrenched in complex neurochemistry when, in 1983, I encountered one of the first girls recognized in the US with Rett syndrome. As such I started a Rett syndrome clinic at the Baylor College of Medicine and recruited Huda Zoghbi to this study as she was completing her child neurology training and moving to advanced training in molecular genetics.

Provide a brief outline of your training and the work you have conducted that has led to this proposal.

I have been involved in clinical research in Rett syndrome since 1984 and have organized and participated in a number of clinical trials since that time. It was recognition that anxiety is increased in these girls and women that led us to treat them with serotonin reuptake inhibitors (SSRIs) and which has led us to attempt this trial to provide justification for its broadened use.

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

The single most rewarding aspect is improving the daily lives of these girls or women and their families.

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

I think this varies with the family and with the age of the child. Probably the most vexing problem for families and physicians is the breathing irregularity that may dominate the lives of many girls and one that may increase dramatically with heightened anxiety. Providing relief for this issue would be life altering for many.

What other disease(s) does your research focus on?

At this point, my research is engaged almost completely in RTT, but I do have an abiding interest in inherited neurodevelopmental and neurodegenerative disorders, particularly those related to sphingolipid metabolism and related leukodystrophies.

Besides your role as principal investigator on this project and as a Rett syndrome investigator, what other roles do you currently hold that are specific to the field of Rett syndrome research?

Currently, I am a member of the IRSF Medical Advisory Board, a grant reviewer for NIH, IRSF, and other agencies or groups as necessary, and I am PI of the Rare Diseases Clinical Research Center grant on Angelman, Rett, and Prader-Willi syndromes.

Provide any other interesting information about yourself or your work that you would like the Rett syndrome community to know about you.

I will soon retire and would like to leave a lasting opportunity in the form of an endowed chair for someone to continue this work at UAB. I would like to see a final resolution of treatment for this disorder, but realize that many steps are required and want to be certain that we provide optimal care until that time.

For more information on Dr. Percy, please visit:

www.mrrc.uab.edu/PI_percy.htm

For a list of Dr. Percy's publications, please visit:

www.ncbi.nlm.nih.gov/pubmed

Investigator Spotlight: Gail Mandel, PhD, Howard Hughes Medical Institute, Vollum Institute, Oregon Health and Science University

IRSF is pleased to highlight Dr. Gail Mandel in this month's Investigator Spotlight. Dr. Mandel recently co-chaired the Basic Research Symposium at the 7th World Rett Syndrome Congress last June alongside Dr. Huda Zoghbi. IRSF is thankful to Drs. Mandel and Zoghbi for putting together an excellent program that will help "Chart the Course" for Rett syndrome research.

Dr. Gail Mandel is a Howard Hughes Medical Institute (HHMI) Investigator, a Senior Scientist at the Vollum Institute, and a Professor in the Department of Biochemistry and Molecular Biology in the School of Medicine at Oregon Health and Science University (OHSU). She received her Ph.D. in Immunology from the University of California, Los Angeles (UCLA) and pursued postdoctoral training at UCLA and the University of California, San Diego. Prior to her position at OHSU, Dr. Mandel had been a faculty member at Harvard Medical School, Tufts University, and Stony Brook University.

In addition to receiving numerous awards throughout her scientific career, Dr. Mandel is a member of the National Academy of Sciences.

Dr. Mandel's laboratory is focused on understanding how cells of the nervous system are established and maintained. They have discovered that this is achieved by molecular mechanisms that include the DNA-binding protein REST, which is central to the regulation of gene expression in the developing nervous system. The Mandel lab has more recently uncovered a role for glial cells in neuronal dysfunction seen in Rett syndrome. They have extended their studies to explore the cell-to-cell interactions between neurons and glial cells and how the glial genes or proteins cause the underlying neuronal pathology.

Dr. Gail Mandel is a member of the IRSF Scientific Advisory Board that serves to help set strategic goals for the advancement of research towards the development of therapeutics for Rett syndrome.

What prompted you to begin a career in research?

Curiosity about how things work in nature.

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

I like to address fundamental questions in biology that may someday have relevance to human disease. I also like to work within a community of scientists whom are passionate about research and set the bar very high. Research in RTT fulfills both of these goals.

What other disease(s) does your research focus on?

With my scientist husband, Paul Brehm, we study zebrafish models of neuromuscular disease and fundamental questions related to how neurons communicate with each and with other cell types.

For more information on Dr. Mandel, please visit:

www.ohsu.edu/xd/research/centers-institutes/vollum/faculty/faculty-profile

www.hhmi.org/research/investigators/mandel_bio

For a list of Dr. Mandel's publications, please visit:

www.ncbi.nlm.nih.gov/sites

Investigator Spotlight: Huda Y. Zoghbi, MD, Howard Hughes Medical Institute, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Baylor College of Medicine

It is hard to believe that the 7th World Rett Syndrome Congress has come and gone with great success! Now with summer upon us, IRSF continues to move the spotlight to the committed scientists who have made the World Congress an impressive, high quality meeting with outstanding presentations and discussions. This month we are honored to focus on Dr. Huda Zoghbi who had co-chaired the Basic Research Symposium at the World Congress along with Dr. Gail Mandel. Together, they had produced an exciting lineup of speakers who were encouraged to present new, unpublished data in an effort to foster new ideas that will help chart the course for Rett syndrome research.

Dr. Zoghbi is a Howard Hughes Medical Institute (HHMI) Investigator, the Director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, and Professor of the Baylor College of Medicine in Houston, TX. She received her medical degree from Meharry Medical College and completed residency training in pediatrics and neurology at Baylor College of Medicine where she encountered her first Rett syndrome patient in 1983. Dr. Zoghbi was inspired to receive additional research training in the area molecular genetics and upon completion she joined the faculty of Baylor College of Medicine.

In 1999, Dr. Zoghbi and collaborators including research fellow Ruthie Amir made a major breakthrough for Rett syndrome. They had discovered that mutations in MECP2, the gene encoding methyl-CpG-binding protein 2, causes Rett syndrome. The discovery that the Rett-causing gene is on the X chromosome proved beyond any doubt that the mostly sporadic Rett syndrome is a genetic disorder and X-linked—a finding that also helps explain why it is usually found primarily in girls.

Dr. Zoghbi and her laboratory use genetic, behavioral, physiological, and cell biological approaches to explore many neurological disorders including the inherited degenerative balance disorders (spinocerebellar ataxias) in addition to Rett syndrome and the MECP2 Duplication syndrome. Their lab has generated a mouse model for Rett syndrome and mice that overexpress MECP2 at twice the normal levels. Studies of these mice and other models have shown that too little or too much MeCP2 can increase phenotypic severity.

In addition to Dr. Zoghbi's role in this year's World Rett Syndrome Congress, she is working on a project titled "Therapeutic Interventions to Modulate the GABAergic System in Animal Models of Rett Syndrome" that was funded by an ANGEL grant awarded to her in 2011. She has made significant contributions for Rett syndrome research and is dedicated to moving research towards treatments and a cure for Rett syndrome. For her noteworthy and admiring dedication, Dr. Zoghbi was presented with the Circle of Angels Award for Outstanding Research in Rett syndrome in 2009.

What prompted you to begin a career in research?

Meeting patients with Rett syndrome.

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

Knowing that the work will help the girls one of these days.

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

Communication. If we can restore or preserve verbal communication I know restoring other deficits will be within reach.

What other disease(s) does your research focus on?

Spinocerebellar ataxia type 1; Shank3 disorders.

Provide any other interesting information about yourself or your work that you would like the Rett syndrome community to know about you.

Reading, working out, gourmet cooking (especially with my daughter, a superb dessert chef), and the opera.

For more information on Dr. Zoghbi, please visit:

www.nri.texaschildrens.org/about_nri/leadership/zoghbi.aspx

www.bcm.edu/genetics/?pmid=11053

www.hhmi.org/research/investigators/zoghbi_bio.html

For a list of Dr. Zoghbi's publications, please visit:

www.ncbi.nlm.nih.gov/pubmed?term=zoghbi%20h20JI

Investigator Spotlight: Jeffrey Neul, MD PhD, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Baylor College of Medicine

With winter having passed by quickly and spring in the air, IRSF is busily preparing for the World Rett Syndrome Congress taking place this June. With that in mind, we are eager to highlight the dedicated scientists who have planned this highly anticipated event to be held for the first time in the US in New Orleans, LA. This month we are pleased to move the spotlight onto Dr. Jeffrey Neul from the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Baylor College of Medicine in Houston, TX. Dr. Neul is the Chair of the Translational and Pre-Clinical Research Symposium at the World Congress. He has put together an exciting program where current knowledge in translational and clinical research on Rett syndrome will be presented and discussion on methods to accelerate these fields will be encouraged.

Dr. Jeffrey Neul is a physician scientist and had received his MD and PhD in Developmental Biology from the University of Chicago. He joined Baylor College of Medicine for a Pediatric Internship and a Residency in Child Neurology. Dr. Neul is now an Associate Professor in the Departments of Pediatrics – Section of Neurology at Baylor College of Medicine. He also holds positions in the Department of Molecular and Human Genetics, Molecular Physiology and Biophysics, and Neuroscience. Dr. Neul is the Anthony and Cynthia Petrello Endowed Scholar of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital. At the Blue Bird Circle Rett Center, he is the Assistant Medical Director and sees patients with Rett syndrome and conducts clinical research on RTT.

In addition to his clinical work, Dr. Neul and his lab are interested in using animal models and molecular techniques to understand the mechanisms that cause some of the specific clinical features found in Rett Syndrome, specifically, in understanding autonomic dysfunction and early death. They have determined that a mouse model reproduces many of

the autonomic abnormalities observed in people with Rett syndrome, including breathing problems and abnormal heart rhythm. Dr. Neul and his lab have recently been awarded a HeART grant for “Pharmacological treatment of cardiac rhythm abnormalities in Rett syndrome”. Dr. Neul also participates in the Natural History Study for Rett syndrome. In conjunction with this study, IRSF will support him to create a DNA repository for Rett syndrome with the goal in mind to identify genetic mutations other than MECP2 that may contribute to the clinical severity of Rett syndrome.

Besides his work in the clinic and the lab, Dr. Neul was a major participant in IRSF's Rett Syndrome Public Service Campaign featuring Clint Black last year. Given his significant contributions towards IRSF's mission to advance research for treatments and a cure for Rett syndrome while improving the overall quality of life for those living with Rett syndrome today, Dr. Neul was awarded the Circle of Angels Award for Outstanding Research in Rett syndrome at the 2011 Rett Syndrome Education and Awareness Conference.

What prompted you to begin a career in research?

As an undergraduate in chemistry, I became fascinated by the way a small ion such as lithium could have a dramatic effect on behavior and mood, which was the beginning of my desire to do neuroscience and be trained as a physician and a scientist. I became specifically interested in Rett syndrome when during my final year of medical school I asked my child neurology mentor, Peter Huttenlocher, where I should train for child neurology. He turned, picked up an open journal lying on his desk, and said “Huda Zoghbi identified the gene for Rett syndrome, so you should go work with her.” It was one of the best pieces of advice any one has every given me.

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

I love working with the children affected with Rett syndrome and thinking about how we can do research to help them live fulfilling lives.

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

If I could, I would try to figure out how to let these children talk. I know they have a lot of things they want to tell their families, and being able to communicate would make a remarkable change in their lives.

Besides your role as principal investigator on this project and as a Rett syndrome investigator, what other roles do you currently hold that are specific to the field of Rett syndrome research?

I am the assistant medical director of the Blue Bird Circle Rett Clinic at Texas Children's Hospital and an investigator on the Rett Syndrome Natural History Study. I am on the IRSF Scientific Review Board and the IRSF Medical Advisory Board, and serve on the FDA Orphan Products Division Grant Review Panel.

Provide any other interesting information about yourself or your work that you would like the Rett syndrome community to know about you.

Outside of the lab and clinic, I spend as much time as possible with my wife and two children. I love bicycling and have participated in the MS150 Houston to Austin ride multiple times.

For more information on Dr. Neul, please visit:

www.bcm.edu/pediatrics/neurology/?pmid=14799

www.bcm.edu/genetics/index.cfm?pmid=13556

For a list of Dr. Neul's publications, please [click here](#).

Investigator Spotlight: Qiang Chang, PhD, University of Wisconsin-Madison

As we enter the New Year, we are pleased to continue highlighting IRSF funded investigators in our Investigator Spotlight series. For the year's first installment, we are thrilled to feature Dr. Qiang Chang from the University of Wisconsin-Madison. Dr. Chang is an Assistant Professor in the Department of Medical Genetics and Neurology. His lab is focused on understanding the molecular mechanism of Rett syndrome and understanding the central role of MeCP2 in DNA methylation-dependent epigenetic regulation of brain development and function.

Dr. Chang received his PhD from the University of Pennsylvania in Neuroscience where he studied the development of motoneurons and neuromuscular junctions in mice in the lab of Dr. Rita Balice-Gordon. He also completed postdoctoral training in Dr. Rudolf Jaenisch's lab at the Whitehead Institute for Biomedical Research/MIT and studied the role of BDNF in RTT disease progression. Today, Dr. Chang's laboratory uses genetic engineering in mouse embryonic stem (mES) cells to manipulate the function of genes that play major roles in establishing and interpreting the epigenetic mark of DNA methylation in vivo, and integrates analyses at the molecular, cellular, electrophysiological, animal behavioral, and genomic levels to study these genetically engineered mice.

To complement their in vivo mouse models, his lab has recently generated isogenic pairs of induced pluripotent stem cell (iPSC) lines from a single female RTT patient carrying the common mutation R294X (5-6% of RTT patients have this mutation), and differentiated both the mutant and wild type iPSC lines into neurons and astrocytes. They are currently using this in vitro system to study RTT disease mechanisms and developing this as a platform for future drug screens. Dr. Chang was recently awarded a 2011 HeART translational grant to support these studies "Establishing Neurons Differentiated from an Isogenic Pair of Rett Syndrome iPSC lines as a Cell-Based Assay for Future Drug Screens".

Dr. Chang was also rewarded a 2008 basic research grant titled "Administering novel small molecules that have been shown to specifically activate TrkB in MeCP2 mutant mice to evaluate the therapeutic potential of BDNF". This work was recently published in the article "7,8-dihydroxyflavone (7,8-DHF) exhibits therapeutic efficacy in a mouse model of Rett syndrome" in the Journal of Applied Physiology. 7,8-DHF is a small molecule reported to activate the high affinity BDNF receptor (TrkB) in the central nervous system. The reported findings indicate the MeCP2 mutant mice that were treated with 7,8-DHF lived significantly longer, had delayed body weight loss, increased neuronal nuclei size, enhanced voluntary locomotor activity, and partially improved in breathing pattern irregularities compared to untreated mutant mice. While the specific mechanisms of 7,8-DHF are not completely known, it appears to reduce disease symptoms in MeCP2 mutant mice and may have potential as a therapeutic treatment for RTT patients.

What prompted you to begin a career in research?

I wanted to do something important and make a difference.

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

The hope that findings from my research will lead to a treatment/cure for Rett girls in the near future.

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

The growth and maturation of the neurons and the brain.

What other diseases does your research focus on?

My research program has a broad interest in neurodevelopmental disorders.

Besides your role as principal investigator on this project and as a Rett syndrome investigator, what other roles do you currently hold that are specific to the field of Rett syndrome research?

NIH grant reviewer, Autism Speaks grant reviewer, European Science Foundation reviewer, journal reviewer.

Provide any other interesting information about yourself or your work that you would like the Rett syndrome community to know about you.

I enjoy playing many sports. Away from science, I spend most of my time raising my two lovely children.

For more information on Dr. Chang, please visit:

www.waisman.wisc.edu/people/pi/Chang_Qiang.html.

For a list of Dr. Chang's publications, please visit:

www.ncbi.nlm.nih.gov.

For more information on the Rett Syndrome Clinic at Montefiore Medical Center, please visit:

www.einstein.yu.edu/neurology/program_details.aspx?id=100180

www.montekids.org/services/leadership/neurology/rett-syndrome/

www.eurekalert.org/pub_releases/2011-12/aeco-nen120111.php

7,8-dihydroxyflavone (7,8-DHF) exhibits therapeutic efficacy in a mouse model of Rett syndrome
Johnson RA, Lam M, Punzo AM, Li H, Lin BR, Ye K, Mitchell GS, Chang Q.

Abstract

Article

IRSF Spotlight: Aleksandra Djukic, MD, PhD, Tri-State Rett Syndrome Center, Montefiore Medical Center, Albert Einstein College of Medicine

To end this year, it is with great pleasure to feature Dr. Aleksandra Djukic in this installment of the Investigator Spotlight series. Dr. Djukic is the Director of the Rett Syndrome Center at the Montefiore Medical Center and is also appointed as an Associate Professor of Neurology at Albert Einstein College of Medicine of Yeshiva University. She attended the University of Belgrade in Yugoslavia-Serbia for both medical and graduate school, received training as a Pediatric Resident and Neurology Fellow at the Albert Einstein College of Medicine in Bronx, NY, and has an extensive background as a neurologist and neuropsychologist.

Dr. Djukic's commitment to Rett syndrome is evident by her vision of developing the Rett Syndrome Center at the Montefiore Medical Center. It was recently announced that the Montefiore Medical Center and Albert Einstein College of Medicine have secured a grant from the National Institute of Neurological Disorders and Stroke (NINDS) to establish a clinical site for the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT). NeuroNEXT was created to facilitate Phase II clinical trials for rare neurological diseases such as Rett syndrome, which face significant challenges securing funding from industry, as well as with recruiting and retaining participants. These additional funds will support the mission of the Rett Syndrome Center to provide state-of-the-art services for patients with Rett syndrome through intervention, education, and research aimed at effective treatments and cures. The specific research goals of the center entail a systematic and uniform documentation of the cognitive phenotype, development of objective outcome measures, and ultimately, development of the approach to education and communication in the Rett syndrome population.

Dr. Djukic has been a long-time advisor for IRSF as a member of the Scientific Review Board and participates on the International Consortium of Rett Syndrome Clinical Researchers (RettSearch). She has also been awarded two HeART awards for her work in developing techniques using eye tracking technology to examine cognitive ability in RTT girls. This translational research will specifically study the ability of these girls to distinguish different emotional expressions, an important aspect of their social skills. Dr. Djukic has also recently received funding from the NIH to study how much RTT girls understand spoken language. Together, these studies are integral components of her mission "to focus on what girls with RTT can do".

In her spare time, she conceived the "Blue Sky Girls" event during October's Rett syndrome awareness month, where the girls and their families gathered together in different parts of the world at the same time to climb to the top of a set of magnificent stairs as a symbolic gesture of overcoming the difficulties they face every minute of their lives. Dr. Djukic, also endearingly called "Dr. Sasha" by her patients and families, is a highly motivated, passionate clinician scientist who treats girls diagnosed with Rett syndrome, performs research to understand their nonverbal cognitive abilities, and raises awareness for Rett syndrome. Thank you, Dr. Sasha, for your dedication to Rett syndrome.

What prompted you to begin a career in research?

My orientation towards research originates in my curiosity to understand how things happen. Understanding how something as abstract as human thought originates from something very physical, the brain, was the main reason I choose to dedicate my professional life to the field of neurology, and focus my research interest on behavioral neurology.

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

As a clinician-scientist, my conviction that clinical and translational research will lead to the substitution of breath holds, anxiety, and pain with smiles in those I deeply care for, and that this will happen in a foreseeable future.

Identify a potential positive outcome of the research you are conducting that is specific to this proposal.

Vision and gaze are considered to be the most important ways in which patients with RTT relate to the world. The objective of this pilot study is to assess visual attention and memory of patients with Rett Syndrome in a structured way, using eye gaze and eye tracking technology. I expect this study to provide better insight into intellectual abilities of individuals with Rett syndrome, to allow physicians and educators to develop more appropriate educational strategies, and provide objective outcome measures for scientists for the upcoming treatment trials.

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

Apraxia, because of its devastating impact on both:

- a. Most fundamental biological functions (feeding, moving)
- b. Most fundamental human functions (speaking).

What other diseases does your research focus on?

Krabbe disease, which is another rare genetic disease which affects children.

Besides your role as principal investigator on this project and as a Rett syndrome investigator, what other roles do you currently hold that are specific to the field of Rett syndrome research?

IRSF Grant Reviewer, RettSearch member.

For more information on Dr. Djukic, please visit:

www.einstein.yu.edu/neurology/faculty_details.aspx?id=9983.

For a list of Dr. Djukic's publications, please visit:

www.ncbi.nlm.nih.gov/pubmed/?term=djukic%20A.

For more information on the Rett Syndrome Clinic at Montefiore Medical Center, please visit:

www.einstein.yu.edu/neurology/program_details.aspx?id=100180

www.montekids.org/services/leadership/neurology/rett-syndrome/

www.eurekalert.org/pub_releases/2011-12/aeco-nen120111.php

For more information on the Blue Sky Girls, please visit:

www.blueskygirlsrett.com

IRSF Spotlight: John Christodoulou, AM, MB, BS, PhD, FRACP, FFSc, FRCPA, CGHGSA, Children's Hospital at Westmead, Sydney, Australia

As we continue with our Investigator Spotlight series, it is our pleasure to highlight Dr. John Christodoulou this month. Dr. Christodoulou is the Director of the Western Sydney Genetics Program, Head of the Genetic Metabolic Disorders Service at the Children's Hospital at Westmead, Sydney, and Professor in the Disciplines of Paediatrics and Child Health and Genetic Medicine at the University of Sydney. He has also been appointed a member of the order of Australia (AM) for his services to human genetics as a researcher and clinician.

Dr. Christodoulou is an extremely active participant in IRSF's research program and has been funded by IRSF since 2002 for the IRSF MECP2 Mutation Database-RettBASE. This database has been constructed by merging mutation and polymorphism data on MECP2 from the published literature pertaining to Rett syndrome and related clinical disorders. This is a freely available resource to researchers and clinicians, with the overall goal of assisting health professionals in providing accurate genetic information to families of children with Rett syndrome.

Dr. Christodoulou also recently participated in the Data Blitz discussion on HDAC inhibitors at the 12th Annual Rett syndrome Symposium this past June. He runs an active laboratory-based and clinical research program, studying Rett syndrome, phenylketonuria (PKU), and the mitochondrial respiratory chain disorders. One of Dr. Christodoulou's current research projects includes the study of the HDAC6 inhibitor Tubastatin A as a potential therapy for Rett syndrome.

What prompted you to begin a career in research?

During my paediatric training, I encountered children with rare genetic disorders for which treatments were either suboptimal or nonexistent. I had always had an interest in basic biology, and in particular, the chemical processes that lead to disease. So I was quick to seize the opportunity to undertake PhD studies in biochemical genetics whilst training in genetics.

Provide a brief outline of your training and the work you have conducted:

I undertook my medical training at the University of Sydney. Following my intern year, I moved to the Royal Alexandra Hospital for Children in Sydney in 1982 where I began my paediatric training. In 1986, my wife and I moved to the Royal Children's Hospital in Melbourne where I undertook advanced training in clinical genetics and where I undertook PhD studies in the field of biochemical genetics. In 1990, we moved to Toronto where I rounded off my postdoctoral clinical and training in biochemical genetics. I returned to Sydney in 1992 to take up an academic position. A year or two later, a serendipitous meeting with Dr. Helen Leonard kindled my interest in the genetics and biology of Rett syndrome, and led me down a committed path of research into the disorder.

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

The notion that by improving our understanding of the biology of Rett syndrome, we may be able to develop specific

targeted therapies to stop progression of the disorder with an ultimate aim of reversing the neurological manifestations of the disorder.

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

It would be spectacular to be able to stop progression of the neurological disorder, or even better, reverse its consequences.

What other disease(s) does your research focus on?

One of my other research interests is study of the biology of the mitochondrial respiratory chain disorders and the discovery of new disease causing genes. Also, we are studying the inborn error of metabolism phenylketonuria (PKU) where we are working on the development of a novel therapy that we hope will reduce the dependence of an onerous protein-restricted diet.

Besides your role as principal investigator on this project and as a Rett syndrome investigator, what other roles do you currently hold that are specific to the field of Rett syndrome research? (i.e. NIH Grant Reviewer, IRSF Grant Reviewer, member of specific Board or Panel, etc.)

I am a NHMRC (National Health and Medical Research Council of Australia) grant reviewer, and have sat on NHMRC genetics grant review panels. In addition, I am an IRSF grant reviewer and a member of the RettSearch executive committee.

Provide any other interesting information about yourself or your work that you would like the Rett syndrome community to know about you.

In my spare time (yeah right!) I try and keep fit by active participation in fencing at my Sydney University club. My favourite weapon is the foil, but will pick up and play with an epee from time to time. Nothing like stabbing at people to unwind!!

For more information on Dr. Christodoulou, please visit:
[br />
sydney.edu.au/medicine/people/academics/profiles/johnch.php](http://sydney.edu.au/medicine/people/academics/profiles/johnch.php).

For a list of Dr. Christodoulou's publications, please visit:

www.ncbi.nlm.nih.gov/pubmed?term=christodoulou%20j.

For more information on the IRSF MeCP2 mutation database-RettBASE, please visit:

mecp2.chw.edu.au/.

IRSF Spotlight: Liang Zhang, MD, PhD, University Health Network, Toronto Western Research Institute

By Janice Ascano, PhD

With the many activities of this past summer, it is a pleasure to welcome the fall and continue with our Investigator Spotlight series. For this month's installment, it is a pleasure to focus on Dr. Liang Zhang from the University Health Network at the Toronto Western Research Institute. Dr. Zhang is an active participant in IRSF's research program, as he recently presented his work at the 12th Annual Rett syndrome Symposium and has been funded by IRSF's translational HeART grant mechanism since 2010. His project titled "Evaluating Carbonic Anhydrase Inhibitors as Potential Treatments for Rett Syndrome" aims to study an anti-convulsive drug (acetazolamide) in its ability to improve the neural and behavioral symptoms in MeCP2-deficient mice. Together with co-investigator Dr. James Eubanks, also at the University Health Network, they will study whether a second drug (valproate) will complement the actions of acetazolamide and increase the overall level of improvement in this RTT mouse model. If the results of this project show significant improvement in these mice, this study will provide the necessary foundation for testing these drugs immediately in Rett patients, as each of these drugs is already approved for clinical use in children.

Dr. Zhang has an extensive background in biomedical research, as he first obtained his medical degree from Wuhan University in China and then became a Lecturer and Assistant Professor in the Department of Medical Physiology at Wuhan University. He developed strong interests in physiology and pathophysiology of the mammalian central nervous system, and pursued a doctorate degree to expand his research capacity. Dr. Zhang obtained his PhD from the Department of Physiology at McGill University in Montreal, and then completed postdoctoral training at the University of Toronto. Dr. Zhang established his own lab and has been working at the Toronto Western Research Institute as a research scientist for the last 15 years.

Dr. Zhang's research focus has expanded to neurophysiology and pathophysiology of behavior in animals. His lab has developed novel techniques that allow chronic monitoring of brain electrical activities from naïve mice and mouse models of neurological disorders. In recent years, Dr. Zhang formed a collaboration with Dr. James Eubanks to examine neurophysiological outcomes in a mouse model of Rett syndrome.

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

The pathophysiology of Rett syndrome is of high complexity. In order to understand the disease process and to design effective treatment strategies for Rett syndrome, it is essential for researchers to consider pathological alterations in multiple organs/systems and at both microscopic and macroscopic levels. In the course of Rett syndrome research, I learned a lot and am still in the learning process as to how to think and operate at macroscopic levels while conducting individual, focused projects.

Identify a potential positive outcome of the research you are conducting that is specific to this proposal.

The focus of our project is to examine whether treatments with the carbonic anhydrase inhibitor acetazolamide alone or together with the anticonvulsant valproate suppress epileptiform brain activity in Rett mice. If so, our project may promote the use of carbonic anhydrase inhibitors as a treatment strategy for Rett syndrome.

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

Rett-associated epileptic seizures.

Besides your role as principal investigator on this project and as a Rett syndrome investigator, what other roles do you currently hold that are specific to the field of Rett syndrome research?

I am an executive member of the University of Toronto Epilepsy Program. I am a primary investigator of two operating

grants from the Canadian Institute of Health Research and the Natural Science and Engineering Research Council of Canada. These grants are aimed to study the cellular and network activities of “normal” and epileptic brains in rodent models.

Provide any other interesting information about yourself or your work that you would like the Rett syndrome community to know about you.

I am a member of the American Epilepsy Society, the American Society for Neuroscience, the Chinese American Association of Biomedical Researchers, and the Canadian League against Epilepsy.

For more information on Dr. Zhang, please visit: [this page](#).

For a list of Dr. Zhang's publications, please visit: [this page](#).

IRSF Spotlight: Yi Eve Sun, PhD, University of California, Los Angeles

By Jim Keller

With this month's installment my goal to expose as many IRSF funded investigators who have a primary role in IRSF's 12th Annual Rett Syndrome Symposium to take place June 26th through 28th at the Lansdowne Resort and Spa in Leesburg, Virginia comes to a close. This month I saw fit to profile one of our meeting Chairs, Dr. Yi Eve Sun from the University of California, Los Angeles who is also a Co-Chair of this year's Session on animal and human cellular models of Rett syndrome (RTT) and is also a 2010 IRSF HeART Grant Award recipient. Her project titled “A high throughput small molecule screening platform for potential Rett Syndrome MBD mutation therapeutics” involves a search for candidate drugs that may enhance the binding of mutant MeCP2 protein to ‘methylated’ DNA. This work is important because RTT mutations frequently arise in the methyl-CpG binding domain (MBD) of the MECP2 gene. Such mutations of the gene are thought to result in the production of a misshapen MeCP2 protein that can no longer bind to methylated DNA. Dr. Sun's drug screen will be conducted using both biochemical test-tube based screens, in combination with cell-culture based screens (using stem cells with common RTT mutations). Taking this approach she hopes, may lead to the discovery of new drugs specifically targeted for individuals with RTT caused by MBD mutations.

Dr. Sun's early work was on the regulation gene expression and more specifically, focused on DNA transcription. DNA transcription is the main mechanism underlying many different events within biological systems in both health and disease. Commenting on her IRSF funded drug screen, Dr. Sun says “Gene regulation has been the [consistent, but] ever changing theme in my studies from the outset of my career as an undergrad and Ph.D. student, a postdoctoral fellow, and now, as an independent principle investigator. This proposal is aimed at finding small molecules that may enable mutated MeCP2 to re-associate with methylated DNA.”

What prompted you to begin a career in research?

Curiosity! I grew up as a kid with enormous curiosity. I still remember the many nights in my childhood when I stood on our balcony staring at the starry night sky, wondering, with passion, what is out there? Then my imagination flew, freely, and far, far away. When I grew up, I thought of becoming an astrophysicist until I found another universe, even more

mysterious, closer yet somehow further away, which sits inside but also connects outside our cranium, to the edge of the universe, the human mind. Like many people, I also wondered how the brain works, and that wonder has grabbed my attention ever since.

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

The hope and belief that we shall be able to help patients, a potentially solvable puzzle.

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

We might be able to find drugs that will be specifically used to enable particular mutant MeCP2 to regain its ability to bind DNA, and therefore restore normal MeCP2 function. Since these mutations result in changes to only a single amino acid, it is possible that it could be a relatively simple problem to "fix" by essentially going around them.

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

There are many candidate drugs I can think of, however, to be able to enable mutant MeCP2 to re-associate with methylated DNA essentially gets to the root of the problem. While it will not work with all kinds of MeCP2 mutations, even if only a subset of patients with particular mutations can be treated, it will be enormously rewarding.

What other diseases does your research focus on?

Parkinson's disease, spinal cord injury, and other autism-spectrum disorders.

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

I am a chartered reviewer for NIH, and I review many RTT-related grants. I also sit on IRSF's Scientific Review Board, and review for many journals on RTT research-related manuscripts.

I like to explore the power and the biology of the human unconscious mind. I am a certified hypno-therapist—though admittedly, I need more time to practice, and I'm currently learning how to ballroom dance. I was once a semi-professional swimmer and springboard-diver as well.

Please visit this page to register for the Symposium and to view a list of confirmed speakers.

IRSF Spotlight: Monica J. Justice, PhD, Baylor College of Medicine

By Jim Keller

This month's installment features Dr. Justice from Baylor College of Medicine who will Co-Chair this year's Session on animal and human cellular models of Rett syndrome (RTT) at our 12th Annual Rett Syndrome Symposium and is also a

2010 IRSF ANGEL Grant Award recipient—the second of its kind. Her project titled “Developing new therapeutic targets for amelioration of Rett Syndrome from the identification of genetic suppressors in mice ” applies cutting-edge techniques to the discovery of suppressors of the symptoms of Rett syndrome. This project uses genetic strategies in mice to identify genes that, when altered, ameliorate the symptoms caused by the mutation of MeCP2. Though Dr. Justice’s approach has had very powerful applications in bacteria, flies and worms, rarely has a forward genetic screen for suppressors been carried out in the mouse (this is only the second one). Despite being considered a very “high risk” screen, her lab’s preliminary data shows that suppressors of the Mecp2 mutation can be identified in the mouse, and suggests that Dr. Justice’s discoveries will have applications for identifying therapeutic targets.

Dr. Justice is considered to be a pioneer in the field of mouse chemical mutagenesis, as she has carried out one of the first such genetic screens as a graduate student at Kansas State University. Her research exploits the fact that genes and whole chromosome regions are conserved between the mouse and human. After completing her postdoctoral training at the National Cancer Institute-Frederick Cancer Research Facility in cancer biology and mouse molecular genetics, Dr. Justice began working in the area of gene discovery where she identified many new cancer-causing genes, as well as new causes of birth defects using genetic and genomic technologies. Her career then followed the wave of genome sequencing and discovering genes and their function. Dr. Justice was Director of a large-scale mutagenesis program in developmental defects, which produced hundreds of new mouse models of human disease that have allowed for discoveries of gene functions in diverse areas such as reproduction, neurobiology, obesity, and blood, heart, and bone development. She was recruited to the RTT field to carry out a genetic screen based on her genetics and genomics expertise.

What prompted you to begin a career in research?

For as long as I can remember, I wanted to help children overcome diseases such as leukemia and cystic fibrosis. My plan was to be a physician, but exposure to a research lab made me realize that research was my passion. My research questions now focus on human health and disease.

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

The possibility that my research could make a difference in the quality of life for girls affected by Rett syndrome drives me. Every discovery and step towards a treatment is a reward. Even so, because our research may directly affect people’s lives, I feel that we cannot carry out our research fast enough!

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

The research I am currently conducting aims to find alternative therapeutic targets for Rett syndrome, which would ameliorate symptoms. We have used a genetic approach to find genes that ameliorate the symptoms in mice, and hope that this knowledge can be applied to humans.

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

My dream is to be able to alleviate the neurological symptoms to an extent that the girls are interactive and healthy. This, hopefully, would mean that they would not have stereotypic movements, seizures, ataxia or breathing disorders. Realistically, any improvement in the quality of life and health of the girls would be a success.

What other diseases does your research focus on?

I am a developmental geneticist. Therefore, the bulk of my research focuses on genetic causes of birth defects and diseases of the blood, including leukemias and blood diseases resulting from hematopoietic stem cell defects. We have created a multitude of mouse models that are being used by many laboratories world-wide.

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

I entered the Rett Syndrome field in 2007 with a high risk genetic project designed to identify modifiers that suppress symptoms of *Mecp2* mutation in the mouse. I am on the IRSF Scientific Advisory Board, an IRSF Grant Reviewer and have Co-Chaired IRSF's Annual Rett Syndrome Symposium. I will be a panelist in an NIH Workshop on "Setting Priorities for Therapy Development in Rett Syndrome."

Working with mice comes naturally to me. I was raised on a farm, and my grandfather and father served as local veterinarians. My uncle is a physician, and my entire family had hoped that I would follow in his footsteps to become a physician. Mouse genetics allows me to combine my ability to work with animals with a direct application to human health. The ability to help children with Rett syndrome has an appeal to me as a person that I have never faced in my role as professor and scientist. Adrian Bird's amazing result, which shows that introducing appropriate levels of *Mecp2* to mice that are severely compromised by disease will reverse the symptoms, allows hope that the symptoms of this genetic disease will be ameliorated in the lifetime of children that are currently affected. Our results will show that such screens can be applied to other genetic diseases that remain untreatable.

Outside of work, I love to garden. I raise my own herbs for gourmet cooking, and I find that cooking after a long day of work relaxes me. My children, grandchildren and husband all appreciate this!

Please visit this page to register for the Symposium and to view a list of confirmed speakers.

IRSF Spotlight: Zhaolan "Joe" Zhou, PhD, University of Pennsylvania, School of Medicine

By Jim Keller

Last month the Investigator Spotlight focused on Dr. Monteggia, an IRSF Regular Research Grant recipient who is also Co-Chairing a Session at our 12th Annual Rett Syndrome Symposium. As the Symposium draws near, I'll be highlighting a key participant in the Investigator Spotlight each month. Dr. Zhou from the University of Pennsylvania, School of Medicine will Co-Chair this year's Session on the regulation and function of MeCP2 and is also a 2010 IRSF Regular Research Grant recipient. His project titled "The study of Rett syndrome with *Mecp2* T158A knockin mice" involves the creation of a Rett syndrome mouse model that recapitulates a common Rett mutation. This new mouse model should provide researchers with a closely relevant platform to understand the molecular basis of Rett syndrome and will be valuable in assessing drug treatments for Rett syndrome.

Dr. Zhou's approach to scientific research has been developed from the valuable experiences he had as a graduate student and as a post-doctoral fellow. While in graduate school, Dr. Zhou was mentored by the legendary molecular biologist, Dr. Tom Maniatis and Dr. Robin Reed. During his graduate studies, Dr. Zhou took on a very challenging project which was previously thought impossible. By developing an ingenious strategy for purifying an important molecular complex within the cell nucleus, he was able to understand important aspects of how the cell's DNA copying process works. As a post-doctoral fellow with eminent neurobiologist, Dr. Michael Greenberg, Dr. Zhou turned his attention to addressing how environment, in the form of experience, modulates MeCP2 protein function, studies which led to the identification of key elements within MeCP2 thought to be responsible for experience-dependent maturation of neuron-neuron connections. This work transformed his research interest from biochemistry to the field of epigenetics and its role in physiology and disease.

Dr. Zhou's laboratory is now focused on understanding the functions of MeCP2 by developing an effective animal model of Rett syndrome, based on commonly occurring mutations seen in the disease. In this case he has developed a mouse model that recapitulates the Mecp2 T158A mutation, allowing researchers in the field to not only study the pathogenesis of the disease, but also to explore potential therapeutic strategies. Recently, Dr. Zhou was also named as a Pew Scholar in Biomedical Sciences and awarded a prestigious Biobehavioral Research Awards for Innovative New Scientists—or BRAINS, from the National Institute of Mental Health (NIMH) to study how environmental factors interact with certain genes to increase the risk of mental illness.

What prompted you to begin a career in research?

It is the fascinating nature of Biology that motivated me to pursue a career in science beginning in my college years.

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

The most rewarding aspect of our research is that our discoveries may lead to a potential treatment or prevention of Rett syndrome in the future.

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

We hope to provide a valid mouse model of Rett syndrome that faithfully recapitulates a Rett mutation. This new mouse model should provide a closely relevant platform to develop and assess therapeutic treatments for Rett syndrome.

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

To prevent or treat the occurrence of seizures.

What other diseases does your research focus on?

Infantile Spasms and Autism.

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

Science education and public awareness are equally as important as our bench research. In my spare time, I like to work with our local Technology Student Association (TSA) to provide guidance and mentorship to high school students by giving feedback to students on their respective science projects. Through this program I hope to help promote science education in public schools.

IRSF Investigator Spotlight: Lisa Monteggia, PhD, University of Texas Southwestern Medical Center

By Jim Keller

As 2011 steps into full swing, Chief Scientific Officer, Dr. Antony Horton and I have been working closely with our Co-Chairs for IRSF's 12th Annual Rett Syndrome Symposium to take place June 26th through 28th at the Lansdowne Resort and Spa in Leesburg, Virginia. This year the symposium will be chaired by Yi Eve Sun, PhD (University of California – Los Angeles) and James H. Eubanks, PhD (University Health Network, Toronto Western Research Institute). Together we identified Session Chairs to help set the agenda and to further the scope and overall impact of our annual meeting. One of our Co-Chairs this year is Dr. Lisa Monteggia from the University of Texas Southwestern Medical Center in Dallas, TX. Dr. Monteggia, an Associate Professor in Psychiatry, is also one of the latest recipients of an IRSF Regular Research Grant as announced last fall. Her project titled "Elucidation of Epigenetic Mechanisms in Rett Syndrome" involves studying changes that occur in neurons as a result of mutations in MeCP2.

Neurodevelopmental disorders such as Rett syndrome (RTT), are thought to be the result of a communication breakdown between neurons. Recent work has shown that a biochemical process called "methylation" provides a way of modifying DNA in order to regulate gene activity and is an important mechanism for fine-tuning how nerve synapses function. If this process is interfered with in any way, it may result in communication breakdown between neurons. This can be best pictured as a broken switchboard where all of the telephone lines are working but not connected properly.

The key enzymes that methylate DNA are called DNA methyltransferases and these form a family of proteins which include the enzymes DNMT1 and DNMT3a. Dr. Monteggia uses a carefully designed strategy that integrates a variety of genetic, behavioral, electrophysiological and optical imaging techniques to examine alterations in DNA methylation via these enzymes. Ultimately she hopes to correct any irregularities in communication breakdown by modifying them with drugs that subtly alter their function thereby fixing the 'switchboard' and restoring communication.

Dr. Monteggia's first research experience was as an undergraduate at the University of Illinois at Urbana. She was initially interested in microbiology, which helped her gain insight into molecular biology techniques. Dr. Monteggia's research interests shifted toward neuroscience, initially while she was employed at Abbott laboratories and later in graduate school. She took advantage of her molecular biology background to examine nerve cell signaling in the central nervous system (CNS). As a postdoctoral fellow, Dr. Monteggia shifted her focus to study the role of the neurotrophin family of proteins, which are important in development and the regulation of mood and antidepressant responses. Her lab's research into Rett syndrome began as she was setting up her lab as an assistant professor and she came across publications from Dr. Huda Zoghbi's laboratory on the identification of the MeCP2 gene with RTT. Neurotrophins are regulated by MeCP2 and Dr. Monteggia thought, here was a devastating disease with clear neuropsychiatric characteristics associated with a single gene. The study of MeCP2 then, represented uncharted territory that could yield novel insight into how gene regulation impacts behavior, and that could possibly be linked to her neurotrophin work. This, she thought, would provide valuable information relevant to the disease process and hopefully a treatment.

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

Working on RTT provides strong motivation that our basic discoveries may find applicability in alleviating suffering induced by this devastating disease.

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

This proposal addresses a fundamental question of how DNA methylation/regulation in mature neurons may impact behavior and neuronal function.

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

Our goal is to define and understand precise synaptic transmission deficits associated with RTT. Our hope is that this endeavor will help alleviate neurological symptoms associated with this disease.

What other diseases does your research focus on?

We are also interested in depression. We are intensively working in identifying novel neuronal signaling pathways that may constitute the basis for better and more effective antidepressants.

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

In addition to conducting research, I am also a member of the Molecular Neuropharmacology and Signaling Study Section (MNPS) and IRSF's Scientific Review Board. I also sit on the Editorial Board of Biological Psychiatry and am the Deputy Editor for Neuropsychopharmacology.

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.

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).

Keerthi Krishnan, PhD of Cold Spring Harbor Laboratory

By Jim Keller

Note: The IRSF Spotlight's intent is to give our lay and scientific communities an idea of who IRSF funded investigators are both as a person and a scientist working to make Research a Reality.

Part of what makes my work at IRSF so enjoyable and worthwhile is the opportunity to interact with young investigators. Whether through meeting them at our annual Rett syndrome Symposium or assisting them with application submission, there's something special about working with the scientists of tomorrow. At any point in their careers these investigators can contribute significantly to developing therapeutics and possibly a cure for this devastating disease. It is for this reason that IRSF's Basic Science Research program includes the Post-doctoral Fellowship Award mechanism—to introduce young investigators to the field of Rett syndrome Research and to facilitate the growth of these investigators into top notch scientists. Through IRSF seed funding, young scientists can begin to publish their research findings and go on to obtain much larger government grants from agencies such as the National Institute of Health (NIH) that help them build their careers, which foster the therapeutics of the future.

Dr. Keerthi Krishnan is one of four young investigators from across the globe that has been chosen for this competitive Award. This year IRSF announced that it would fund Dr. Krishnan's grant titled "Role of MeCP2 in the maturation of neocortical GABA interneurons and critical period of plasticity" as part of its 2010 Basic Science Research grant funding.

Brain function involves networks of neurons communicating with each other, using chemicals called neurotransmitters to send signals. These can be excitatory "on" signals or inhibitory "off" signals and GABA is one of the major neurotransmitters used to send an "off" signal. Dr. Z. Josh Huang is a world leader in the study of GABA neurotransmission in the brain neocortex. His lab at Cold Spring Harbor, New York, examines how the neuronal connections using GABA are formed and how they are changed during brain development into the mature pattern. It is believed that many brain connections do not reach the correct mature pattern in Rett syndrome. Dr. Krishnan will work under Dr. Huang's direction, to study the role of MeCP2 in the maturation of GABA connections in the neocortex and how the maturation changes as a consequence of the MeCP2 mutation in Rett syndrome. This could provide targets for interventions to correct the maturation.

Dr. Krishnan graduated from the University of Illinois, Urbana-Champaign in 1998 and later went on to work as a research technician for three years at the University of California, San Francisco. In 2002, she became a graduate student at the department of Pharmaceutical Sciences and Pharmacogenomics. Dr. Krishnan's thesis work involved determining the molecular mechanisms of early brain formation in zebra fish. For her post-doctoral work, she wanted to work in a lab where basic research knowledge could be easily translated to a neurodevelopmental disease model that could eventually lead to therapeutic benefits. To follow this path, Dr. Krishnan uprooted herself and moved across the country to the northern part of Long Island where she started her post-doctoral training at Cold Spring Harbor Laboratory under the direction of Dr. Huang. Once there, she studied the molecular changes in the GABAergic system in the Rett Syndrome mice model, which led her to apply for IRSF funding.

What prompted you to begin a career in research?

As a pre-med major in college, I volunteered to work in a research lab for two years to gain a better understanding of the scientific process that eventually leads to medicinal cures. Once I started along this route, I realized that this career path was much more satisfying and better suited for my personality.

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

The possibility of therapeutic intervention for this disease.

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

The expected results from my research will provide us with a new model and/or framework, which might lead us to more and/or better drug targets earlier on.

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

Cognitive deficits

What other diseases does your research focus on?

My research is focused specifically and entirely on Rett syndrome.

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

I trained for several years in a classical, South Indian dance form called Bharathanatyam and enjoy dancing when I have the opportunity.

Carla J. Shatz, PhD of Stanford University

By Jim Keller

Note: The IRSF Spotlight's intent is to give our lay and scientific communities an idea of who IRSF funded investigators are both as a person and a scientist working to make Research a Reality.

Last year IRSF had the privilege to host distinguished neuroscientist, Dr. Carla J. Shatz of Stanford University as its Keynote Speaker for the Foundation's 10th Annual Rett Syndrome Symposium. At the meeting Dr. Shatz, Professor of Biology and Neurobiology who currently serves on the National Advisory Council of the National Institute of Mental Health, discussed how interactions between neural activity and newly-discovered neuronal genes shape and fine-tune brain circuit formation. In October, the Foundation announced that her Research Grant titled "MHC Class I molecules and receptors as therapy for Rett syndrome?" was selected as part of its 2010 grant funding that totals \$2.15 million. Dr. Huda Zoghbi, who discovered the gene responsible for Rett syndrome, expressed her enthusiasm, "I am thrilled to learn that Dr. Shatz will examine visual system plasticity in a mouse model of Rett syndrome. Bringing Carla into the Rett syndrome field is a huge boost to the neurobiological studies on this disorder." With this Award, made in honor of Grace Reddington, Dr. Shatz becomes one of the latest additions to a long line of distinguished IRSF funded investigators.

Dr. Shatz did her graduate training at Harvard Medical School where she was mentored by the Nobel Laureates, David Hubel and Torsten Wiesel. Drs. Hubel and Weisel were pioneers in the study of how experience influences brain development, showing how early visual experience guides development of the visual system. Dr. Shatz's studies have focused on how this influence is accomplished. Even her first studies had immediate impact resulting in her receiving the Society for Neuroscience (SFN) Young Investigator Award in 1985. Her studies have continued to define key mechanisms and shown how experience changes the relatively imprecise early connections between neurons in brain and refines them into adult precision. A recent research discovery is that a family of molecules (MHC Class I family) previously considered for their role in immune recognition were found to also play a key role in controlling the plasticity involved in experience induced changes in brain connections. This mechanism may not only contribute to regulating brain wiring during critical periods of development but also for learning and memory in the adult. This discovery establishes a potential route for immune-neuronal interactions and opens new doors for understanding how genes and environment may interact in complex neurological disorders such as Autism. MeCP2, a gene mutated in Rett syndrome, also contributes to experience mediated refinement of connections during brain development. IRSF is excited to have Dr. Shatz turn her attention to Rett syndrome and investigate if modulating the MHC class of enzymes could compensate for reduced or lost MeCP2 function in Rett syndrome.

Dr. Shatz has received countless Awards and has enjoyed membership in numerous prestigious scientific organizations including the Institute of Medicine and has held the title of President of the Society for Neuroscience. She graduated from Radcliffe College with a B.A. in Chemistry and was honored with a Marshall Scholarship to study at University College London, where she received an M.Phil. in Physiology. Dr. Shatz went on to receive her Ph.D. in Neurobiology from Harvard Medical School where she completed her postdoctoral training with Dr. Pasko Rakic in the Department of Neuroscience. In 1978, Dr. Shatz moved to Stanford University, where she became Professor of Neurobiology and ultimately moved her lab to the University of California, Berkeley, where she was Professor of Neurobiology and an Investigator of the Howard Hughes Medical Institute (HHMI). She assumed the role of Department Chair of Neurobiology at Harvard in 2000 as the Nathan Marsh Pusey Professor of Neurobiology and returned to Stanford in 2007 as Director of Bio-X.

What prompted you to begin a career in research?

A dual love of science and art brought me to a synthesis of both in graduate school, where I began my studies of the function and development of the visual system. I had no interest in going to medical school at that time--I was excited by the newly-created field of neurobiology, and I was also disappointed that neurologists had little to offer patients in the way of treatments or cures for almost all neurological disorders, including the stroke that my grandmother had just suffered.

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

The idea that our research may contribute key knowledge about the underlying mechanism of this devastating developmental disorder, and that this mechanistic understanding may lead not only to treatments but also to cures.

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

We hope to find molecules and mechanisms that reveal new opportunities for developing drugs or other therapeutic approaches

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

Perhaps this is a naive goal, but I would like to contribute research and understanding of mechanism that could someday result in a treatment of global symptoms.

What other diseases does your research focus on?

My research is focused on elucidating fundamental mechanisms of how experience and neural activity alter brain circuits, especially during early critical periods of development and learning. My lab conducts basic neuroscience research, not clinical research. Because we've discovered an unexpected role for immune molecules in brain plasticity, our research may be relevant to a broad range of disorders in which inflammation and the immune system are suspected as contributors, including not only Autism and Schizophrenia, but also possibly even neurodegenerative disorders such as Alzheimer's.

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

I have no hobbies at present and work almost all the time. This is not healthy but I am enjoying myself. In addition to research in my own lab, I am Director of Bio-X, an exciting experiment in interdisciplinary research at Stanford aimed at breaking down the ivory towers that act as barriers separating different fields and aimed at bringing together scientists, engineers and clinicians from many disciplines to tackle the challenge of understanding life's complexity and of repairing the body and brain.

John M. Bissonnette, MD of Oregon Health and Science University

October 11, 2010

By Jim Keller

Note: The IRSF Spotlight's intent is to give our lay and scientific communities an idea of who IRSF funded investigators are both as a person and a scientist working to make Research a Reality.

Last week IRSF reported on a study published in the journal, Proceedings of the National Academy of Sciences, which focused on how a team of researchers based in the U.S. and UK revealed that they were able to halt the potentially lethal, breath holding episodes associated with Rett syndrome. These investigators were none other than Dr. John M. Bissonnette and his collaborator Dr. Julian FR Paton of the University of Bristol, co-Principal Investigators (co-PIs) on the recently announced IRSF Research Grant, titled "Pharmacological treatment of respiratory disorders in a mouse model of Rett syndrome." In addition, Dr. Bissonnette was also the recipient of one of the first IRSF Help Accelerate Rett Therapeutics (HeART) Awards, titled "Serotonin and small molecule treatment of respiratory disorders in a mouse model of Rett syndrome," and is a member of IRSF's Scientific Review Board (SRB). With his numerous contributions to the Rett community, we thought it was time to introduce Dr. Bissonnette who was kind enough to answer a few questions on the eve of Rett syndrome Awareness Month.

Dr. Bissonnette studied medicine at McGill University in Montreal, Canada, during which he spent a month in a basic research lab as a first year student. He was assigned to a group working on encephalitis, which served as his introduction to the central nervous system. As a resident he again had basic research exposure examining acid-base regulation in rhesus monkey fetuses. Following a post-residency fellowship, Dr. Bissonnette established a laboratory that studied control of respiration in fetal sheep until 1997, when the lab redirected to work with mice to take advantage of mouse genetics. RTT mice are unique in that they have a high incidence of spontaneous apneas and may lead to a greater understanding of a broad range of respiratory control disorders.

What prompted you to begin a career in research?

After I had finished my clinical training I was a post-doctoral fellow in a cardiorespiratory physiology laboratory. I became captivated by the process of moving from experimental data to concepts of "how things work" and that process remains after many years.

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

For the first time in my research career I am working on an animal model of a human disorder.

What is a potential positive outcome of the research you are conducting that is specific to your latest IRSF Awards?

There are two arms to our current program. In one, we are attempting to identify the location within the respiratory network (that has a number of centers distributed within the pons, medulla and cervical spinal cord) where excess activity of expiratory neurons reside. At present, we are focused on the Kölliker-Fuse nucleus in the pons. We are looking at the inhibitory synapses that attach to Kölliker-Fuse neurons.

The second arm of our research may lead to treatment of respiratory disorders in RTT. We recently found that serotonin 1a receptor agonists markedly reduce apnea in RTT mice and restore regularity to their breath cycle. The pharmacological agent used, however, is not clinically available. We are now testing an alternate serotonin 1a agonist, Sarizotan. Sarizotan has been used in phase 2 human trials to treat levo-dopa-induced dyskinesia in Parkinson's disease. If successful it could advance to clinical testing more rapidly than an untried drug.

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

From my limited clinical observations I would look for relief of the purposeless body movements.

What other disease(s) does your research focus on?

RTT is the only mouse model that we are studying, but an understanding of the basis for respiratory disturbances in RTT may have wider implications.

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

When not in the lab I enjoy hiking in the many mountain areas available in Oregon. Weather permitting, I bicycle to the lab. At home I enjoy cooking and walking our Labrador-mastiff mix dog. Also, I have been privileged to have Sharon Knopp as my laboratory associate for over 25 years.

