

**2009 International Tuberous Sclerosis Complex Research Conference:
From DNA to Human Therapies
Final Report**

The Tuberous Sclerosis Alliance is honored to provide this final report for the 2009 International Tuberous Sclerosis Complex (TSC) Research Conference that was supported by Grant No. 1R13NS66640-1 to Vicky H Whittemore. We have provided this document as the final report, and we will also mail this report along with the CD that contains the entire conference program including abstracts the NIH Central Processing Center. The Tuberous Sclerosis Alliance thanks all of the NIH Institutes that provided funding for this conference.

Overview

The Tuberous Sclerosis Alliance organized an International Tuberous Sclerosis Complex (TSC) Research Conference that took place on September 23-26, 2009 at Indian Lakes Hilton Resort in Bloomingdale, IL. Attended by 150 participants from 14 countries (including Australia, Canada, China, England, Germany, Italy, Japan, Macedonia, The Netherlands, Northern Ireland, Norway, Scotland, Sweden, and the USA), the participants included physicians, genetic counselors, nurses, basic researchers, clinical researchers, parents of individuals with TSC, and industry representatives. It was exciting to see the interactions between all of those attending the conference.

John Blenis, PhD from Harvard University summarized his impression of the conference by saying, "As someone doing very basic research, it is exciting for me to see how the work in my community has had such a broad and positive impact on Tuberous Sclerosis and LAM. I absolutely love hearing about all the current mouse model systems, the clinical trials and the positive effects that rapamycin is having on some of the symptoms associated with TSC and LAM. Hearing the families speak has a tremendous effect on me personally and reinforces my enthusiasm for driving forward to identify additional therapeutic targets in the mTOR pathway as well as other pathways that contribute to these diseases."

Conference Organizing Committee

The Conference Organizing Committee included the following individuals:

- Aristotelis Astrinidis, PhD, Drexel University, Philadelphia, PA
- Sandra Dabora, MD, PhD, Brigham & Women's Hospital, Boston, MA
- Kari Luther Carlson, Tuberous Sclerosis Alliance, Silver Spring, MD
- Petrus de Vries, MD, PhD, University of Cambridge, Cambridge, UK
- Kevin Ess, MD, PhD, Vanderbilt University, Nashville, TN
- Michael Gambello, MD, PhD, University of Texas Health Science Center, Houston, TX
- Arnold Kristoff, MD, McGill University, Montreal, Canada
- Brendan Manning, PhD, Harvard School of Public Health, Boston, MA
- Brenda Porter, MD, PhD, Children's Hospital of Philadelphia, Philadelphia, PA
- Mustafa Sahin, MD, PhD, Boston Children's Hospital, Boston, MA
- Katie Smith, Tuberous Sclerosis Alliance, Silver Spring, MD
- Andrew Tee, PhD, Cardiff University, Cardiff, UK
- Vicky Whittemore, PhD, Tuberous Sclerosis Alliance, Silver Spring, MD
- Michael Wong, MD, PhD, Washington University, St. Louis, MO
- Joyce Wu, MD, University of California, Los Angeles, Los Angeles, CA

These individuals assisted with formulating the agenda, identifying and inviting speakers, reviewing abstracts submitted for presentation and/or the poster session, and serving as chairs for the sessions.

Travel Awards

Travel Awards were provided to 11 people based on review of their submitted abstract. Each predoctoral student, postdoctoral fellow or junior faculty person was provided with a scholarship of \$1,000 that could be used to cover the expenses for conference registration, hotel costs and/or travel expenses. The individuals who were provided Travel Awards were:

- Cleo Bonnet, PhD, Cardiff University, Cardiff, UK
Defects in Cell Polarity Underlie TSC-and ADPKD-associated Cystogenesis
- Lisa Clayton, BSc, University College London, London, UK
Optical Coherence Tomography in Patients Taking Vigabatrin: Exploring New Methods to Assess Visual Field Loss
- Christian Dibble, PhD, Harvard School of Public Health, Boston, MA
Characterization of mTORC2 Regulation Through Rictor Phosphorylation: Identification of an IRS1-independent Feedback Mechanism
- Kayleigh Dodd, BSc, Cardiff University, Cardiff, UK
Modulation of Hypoxia Inducible Factor-1-Alpha
- Jennifer Flinn, BA Hons, BEd, Master's of Education, University of Western Ontario, Ontario, Canada
Tuberous Sclerosis Complex in the Classroom: Implications for Teaching and Learning
- Laia Gómez, PhD Student, Catalan Institute of Oncology, Barcelona, Spain
TACC3-TSC2 Maintain Nuclear Envelope Structure and Control Cell Division
- Susan Goorden, MSc, Erasmus Medical Center, Rotterdam, the Netherlands
The Generation and Characterization of a Rheb Knock Out Mouse
- Birte Japs, BS, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany
Learning and Memory in TSC2+/- (Eker) Rats Challenged With Experimental Epilepsy
- Rajesh Thangapazham, PhD, Uniformed Services University of the Health Sciences, Bethesda, MD
Cellular Targets of Rapamycin in a Xenograft Model of TSC Skin Tumors
- Mark Zervas, PhD, Brown University, Providence, RI
Effects of Conditionally Inactivating *Tsc1* in the Thalamus During Development in a Mouse Model of Tuberous Sclerosis

Goals of the Conference

The overarching goal of the conference was to bring together researchers and health care professionals to discuss our current knowledge of the underlying mechanisms that cause the various manifestations of TSC and what research is needed in the future. There has been a tremendous focus on the role of the TSC1 and TSC2 genes in the mTOR cell signaling pathway, so one of the goals was to discuss whether or not a defect in this signaling pathway explains all of the manifestations of TSC. The speakers who participated in each session were specifically chosen so that the goals outlined for each session in the R13 application could be met.

Final Agenda and Speakers

The Final Agenda including the speakers and the titles of their presentations is listed below. The conference agenda was designed to meet the goals for each session,

provide ample time for discussion, and to allow time for a poster session so that all participants could present their research.

**International Tuberous Sclerosis Complex (TSC) Conference: From DNA to Human Therapies
Final Agenda**

Wednesday, September 23, 2009

12:00 pm – 9:00 pm Registration Open – Conference Center Registration Desk

Dinner on your own

**Opening Session: An Overview of TSC and the mTOR Pathway
Trillium 1 & 2
Chair: Vicky Whittemore, PhD**

6:30 pm – 7:30 pm Opening Reception – Trillium 3 & 4

7:30 pm – 9:00 pm Welcome and Introductions – Kari Luther Carlson, President & CEO, and Celia Mastbaum, Board Chair, Tuberous Sclerosis Alliance

Pathological and Therapeutic Implications of mTOR Misregulation in TSC
Brendan Manning, PhD, Harvard School of Public Health, Boston, MA

Thursday, September 24, 2009

7:00 am – 10:00 pm Registration Open - Conference Center Registration Desk

7:30 am – 8:30 am Breakfast – Trillium 3 & 4

**Session I: Models and Mechanisms of TSC Pathology: Non-CNS
Trillium 1 & 2
Session Chair: David Kwiatkowski, MD, PhD**

8:30 am – 8:40 am Simona Bellagambi – Perspective from the Aunt of a Child with TSC

8:40 am – 9:40 am mTOR Signaling and Cancer
John Blenis, PhD, Harvard Medical School, Boston, MA

9:40 am – 10:05 am Function of the TSC-mTOR Pathway in Energy Balance
Kun-Liang Guan, PhD, University of California, San Diego

10:05 am – 10:30 am Mechanisms and Therapeutic Implications of AMPK Regulation of mTORC1 Signaling
Reuben Shaw, PhD, Salk Institute, La Jolla, CA

10:30 am – 10:45 am Break – Trillium 3 & 4

10:45 am – 11:05 am Characterization of mTORC2 Regulation Through Rictor Phosphorylation: Identification of an IRS1-independent Feedback Mechanism
Christian Dibble, Harvard School of Public Health, Boston, MA

11:05 am – 11:25 am Defects in Cell Polarity Underlie TSC-and ADPKD-associated Cystogenesis
Cleo Bonnet, PhD, Cardiff University, Cardiff, UK

- 11:25 am – 11:45 am *TSC2*+/- Mice Develop Tumors in Multiple Sites Due to the Activation of the Mesenchymal-specific Gene *Hmga2*
Kiran Chada, PhD, University of Medicine and Dentistry, Robert Wood Johnson Medical School, NJ
- 11:45 am – 12:05 pm An Epigenetic Event May Underlie the TSC Features in TSC2 ASM Cells
Elena Lesma, PhD, Università degli Studi di Milano, Milano, Italy
- 12:05 pm – 12:25 pm TSC Missense Variants and Their Role in Disease
Rosemary Ekong, PhD, University College London, UK
- 12:25 pm – 1:30 pm Lunch – Trillium 3 & 4

**Session II: Models and Mechanisms of TSC Pathology: CNS
Trillium 1 & 2
Session Chair: Brenda Porter, MD, PhD**

- 1:30 pm – 1:40 pm Lori Iverson – Perspective from the Mother of a Child with TSC
- 1:40 pm – 2:40 pm Mouse Models as Translational Tools to Discover Treatments for Autism Spectrum Disorders: Focus on Rapamycin
Luis Parada, PhD, University of Texas Southwestern Medical School, Dallas, TX
- 2:40 pm – 3:05 pm Axonal Connectivity in Tuberous Sclerosis Complex
Mustafa Sahin, MD, PhD, Boston Children's Hospital, Boston, MA
- 3:05 pm – 3:30 pm The Neurodevelopmental Pathology of a Mouse Model in TSC
Michael Gambello, MD, PhD, University of Texas Health Science Center, Houston, TX
- 3:30 pm – 3:45 pm Break – Trillium 3 & 4
- 3:45 pm – 4:05 pm Defects of Neural Development and Cell Size in a Zebrafish Model of Tuberous Sclerosis Complex
Kevin Ess, MD, PhD, Vanderbilt University, Nashville, TN
- 4:05 pm – 4:30 pm Glutamate transport and potassium uptake are impaired in astrocytes in human epileptic tuberous sclerosis tissue
Guy McKhann, MD, Columbia University, New York, NY
- 4:30 pm – 4:50 pm Regulable Loss of TSC1 in Neural Progenitor Cells Yields a Model of Tuberous Sclerosis Complex (TSC) with Giant Cells and Other Features Replicating Cortical Tubers
June Goto, PhD, Brigham and Women's Hospital, Boston, MA
- 4:50 pm – 5:10 pm The Generation and Characterization of a Rheb Knock Out Mouse
Susan Goorden, MSc, Erasmus Medical Center, Rotterdam, the Netherlands

Poster Session

- 5:30 pm – 7:30 pm Wine & Cheese Reception and Poster Session – Cyperus 1 & 2
- 7:30 pm – 9:30 pm Dinner – Trillium 3 & 4

Friday, September 25, 2009

- 7:00 am – 7:00 pm Registration Open - Conference Center Registration Desk
- 7:30 am – 8:30 am Breakfast – Trillium 3 & 4

Session III: Brain Development, Epileptogenesis and Neurocognition

Trillium 1 & 2

Session Chair: Joyce Wu, MD

- 8:30 am – 8:40 am Svein-Erik Bakke – Perspective of a Father of a Child with TSC
- 8:40 am – 9:40 am The Neurology of Tuberous Sclerosis Complex: Epilepsy, Cognition and Behavior
Elizabeth Thiele, MD, PhD, Massachusetts General Hospital, Boston, MA
- 9:40 am – 10:05 am Designing Rational Therapies for Epilepsy in TSC
Michael Wong, MD, PhD, Washington University, St. Louis, MO
- 10:05 am – 10:30 am Defining the Seizure Focus in Children with Tuberous Sclerosis Complex
Howard Weiner, MD, New York University, New York, NY
- 10:30 am – 10:45 am Break – Trillium 3 & 4
- 10:45 am – 11:10 am Molecular, Synaptic, and Behavioral Abnormalities in Dominant/Negative TSC2 Mice
Eric Klann, PhD, New York University, New York, NY
- 11:10 am – 11:30 am Effects of Conditionally Inactivating *Tsc1* in the Thalamus During Development in a Mouse Model of Tuberous Sclerosis
Mark Zervas, PhD, Brown University, Providence, RI
- 11:30 am – 11:55 am Context-dependent Functions of PI3K Signaling in the Nervous System
Suzanne Baker, PhD, St. Jude's Children's Hospital, Memphis, TN
- 11:55 am – 12:20 pm Translational Neuroscience in TSC- Are We at Risk of Getting Lost Between the Bench and the Bedside?
Petrus de Vries, MD, PhD, University of Cambridge, Cambridge, UK
- 12:20 pm – 1:30 pm Lunch – Trillium 3 & 4

Session IV: Current and Future Therapeutic Options for TSC and Related Disorders

Trillium 1 & 2

Session Chair: Aris Astrinidis, PhD

- 1:30 pm – 1:40 pm Debora Moritz – Perspective of a Mother of a Child with TSC
- 1:40 pm – 2:40 pm Treating Tuberous Sclerosis: Understanding Its Biology Strengthens Our Hand
Julian Sampson, MB, Cardiff University, Cardiff, UK
- 2:40 pm – 3:05 pm Therapeutic Options and Biomarkers for TSC Related Tumors: Rapamycin, VEGF-D, and Angiogenesis Inhibitors
Sandra Dabora, MD, PhD, Brigham & Women's Hospital, Boston, MA
- 3:05 pm – 3:30 pm TSC Renal Disease: Novel Features and Implications
John Bissler, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
- 3:30 pm – 3:45 pm Break – Trillium 3 & 4
- 3:45 pm – 4:05 pm Clinical Trials of mTOR Inhibitors for TSC and LAM
David Franz, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

- 4:05 pm – 4:30 pm Epilepsy in TSC: How Early Can We Treat It?
Sergiusz Jozwiak, MD, PhD, Children's Hospital, Warsaw, Poland
- 4:30 pm – 4:50 pm Optical Coherence Tomography in Patients Taking Vigabatrin: Exploring New Methods to Assess Visual Field Loss
Lisa Clayton, BSc, University College London, London, UK
- 4:50 pm – 5:10 pm Cellular Targets of Rapamycin in a Xenograft Model of TSC Skin Tumors
Rajesh Thangapazham, PhD, Uniformed Services University of the Health Sciences, Bethesda, MD
- 7:00 pm – 9:00 pm Conference Dinner – Trillium 3 & 4

Saturday, September 26, 2009

- 7:00 am – 12:00 pm Registration Open - Conference Center Registration Desk
- 7:30 am – 8:30 am Breakfast – Trillium 3 & 4

Session V: Does Aberrant mTORC1 Signaling Explain Everything? Trillium 1 & 2 Session Chair: Cheryl Walker, PhD

- 8:30 am – 8:40 am Lisa and Rob Moss – Perspectives of Parents of a Child with TSC
- 8:40 am – 9:40 am Tuberos Sclerosis and LAM: Pathogenic Mechanisms
Elizabeth Petri Henske, MD, Brigham & Women's Hospital, Boston, MA
- 9:40 am – 10:05 am Pathogenesis of TSC through Epithelial Mesenchymal Transition (EMT)
Raymond Yeung, MD, University of Washington, Seattle, WA
- 10:05 am – 10:30 am Regulation of Signal Transducer and Activator of Transcription-1 (STAT1) by Mammalian Target of Rapamycin
Arnold Kristof, MD, McGill University, Montreal, Quebec, Canada
- 10:30 am – 10:45 am Break – Trillium 3 & 4
- 10:45 am – 11:05 am 4-Phenylbutyric Acid: An AMPK Agonist and mTORC1 Inhibitor
Lawrence Quilliam, PhD, Indiana University School of Medicine, Indianapolis, IN
- 11:05 am – 11:25 am Pharmacologic Inhibition of Polo-like Kinase 1 (PLK1) Decreases the Survival of Hamartin and Tuberin Deficient Cells
Aristotelis Astrinidis, PhD, Drexel University College of Medicine, Philadelphia, PA
- 11:25 am – 11:55 am TACC3-TSC2 Maintain Nuclear Envelope Structure and Control Cell Division
Laia Gomez, Catalan Institute of Oncology, Barcelona, Spain
- 12:00 pm Conference Adjourns

Scientific highlights of the conference include:

- As more details are identified about the role of the TSC1/2 complex regulation of mTOR, there are some functions that are sensitive to mTOR inhibitors, and some that are not. The details of the regulation of the pathway and the role of the mTOR inhibitors will be critical to understanding how to best treat the clinical manifestations of TSC.
- In addition to blocking aberrant mTOR signaling, mTOR inhibitors (like rapamycin) also relieve stress on cells – actually making them more resistant to cell death. This mechanism will need to be taken into account in developing targeted treatments for the tumors in TSC that will shrink and kill the tumor cells while not affecting the rest of the body.
- Certain genes are apparently not affected by rapamycin and there are resistance mechanisms, suppressive feedback loops, and differential effects on protein synthesis. mTOR inhibitors may also activate pathways that we don't want activated, so this will need to be taken into account when developing treatments.
- Cells are very vulnerable when they enter the cell cycle (leading to cell division). The clinical trials have shown that the renal angiomyolipomas (AMLs) shrink while the individuals is taking an mTOR inhibitor, but regrow back to baseline size or larger once the medication is stopped. By removing the mTOR inhibitor, cells enter a period of rapid growth where they may be particularly vulnerable to being killed by adding the right agent. This could be a very exciting avenue of pursuit for targeted treatment of tumors in TSC.
- As we understand TSC more, it's evident that mental health issues are a significant problem for individuals with TSC. 66% have one or more psychiatric symptoms and 37% have 2 or more. The most common ones are mood disorder, anxiety, ADHD, aggressive behavior, self injurious behaviors - the last one, suffered by 10%, is associated with infantile spasms, autism and intellectual disability.
- Harvard has found that 1/3 of those with refractory epilepsy become seizure-free on the Ketogenic diet, or on the low glycemic index diet. This works by starving the affected pathway and is being used in treatment for some cancers, Alzheimers and Parkinsons. However, 60% of those on the ketogenic diet had growth in TSC lesions. However, there is early promising evidence that the low glycemic index diet avoids this negative consequence.
- Not all brain tubers are created equal, and evidence from studies funded by the TS Alliance, there are very small collections of abnormal cells (microtubers) around the area of tubers that are likely involved in causing seizures. Also, some tubers become cyst-like over time – seen in 46% of the MRIs reviewed at Mass. General Hospital.
- There were several new animal models of TSC presented that focus on brain function including epilepsy and learning and memory. Important insights into the development of the brain and abnormalities in development when there are mutations in the TSC genes will guide future studies to understand the cause(s) of cognitive deficits, intellectual disabilities and psychological and psychiatric issues in individuals with TSC.
- Most SEGA reduction happens in the 1st 3 months of being on the mTOR inhibitor RAD001, or Everolimus, and then the rate slows down. CSF obstruction is relieved with the reduction of SEGA, those with inoperable SEGA's have shown significant improvement, and partial seizure activities decreased by 87% (based on EEGs). Without a control group (all received the drug), it is difficult to know how much of the improvement in seizure control was a direct result of the medication versus as a consequence of reduced intracranial pressure due to the tumor shrinkage and reduction of hydrocephalus. The current clinical trials sponsored by Novartis Oncology will answer these questions.
- Dr. Jozwiak from Warsaw, Poland, showed that if he closely monitors infants diagnosed with cardiac rhabdomyomas and/or with TSC prior to the onset of seizures he can detect the development of an abnormal EEG prior to the onset of clinical seizures. He has treated those infants who develop abnormal EEGs with vigabatrin, and reports a huge difference in

outcomes with this approach. This controverts previous clinical protocol of treating seizures, not the EEG.

- New visual field studies were reported using optical coherence tomography which measures the thickness of the Retinal Nerve Fiber Layer. A thinner layer correlates with visual field loss, and it might be a more accurate measure of peripheral vision loss than the conventional visual field test, which is more difficult to do on TSC persons with cognitive or attention impairment. Results show that only about 1/3 retain normal peripheral vision, though the extent of loss is the key issue.

In conjunction with the conference, the TS Alliance organized an Industry Roundtable Discussion that focused on what should the next clinical trial in TSC be focused on? Three key themes emerged from the Roundtable discussion as priority needs in our path to a cure:

- A drug-screening program for testing potential new treatments in model systems prior to moving them on to clinical trials in individuals with TSC;
- A Clinical trials network so that new clinical trials can be launched quickly and efficiently nationwide;
- Design family-centered clinical trials to encourage more participation. The lack of enrollment and slow enrollment in clinical trials is and will continue to inhibit progress towards a cure!

Conference Sponsors

The R13 was funded by the National Institute of Neurological Disorders and Stroke; National Cancer Institute; Office of the Director, Office of Rare Diseases; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Arthritis and Musculoskeletal and Skin Diseases; and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health. In addition, conference sponsorship was obtained from Novartis Oncology, Athena Diagnostics, Cyberonics and Lundbeck Inc.

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