2023 International TSC Research Conference: Fueling the Future

Research Conference Summary

The 2023 International TSC Research Conference: *Fueling the Future* was held at the Omni Shoreham Hotel in Washington, DC from September 7-9, 2023. The conference was hosted by the TSC Alliance and welcomed 256 participants from 25 different countries. Importantly, 15% of attendees self-identified as members of groups historically underrepresented in biomedical research. Thirty oral presentations, 59 poster presentations, and 4 breakout discussion groups promoted collaborative discussions between scientific researchers, health care professionals and members of the TSC community. To conclude the event, a joint session was held with individuals and families attending the Regional TSC and LAM conference to convey the importance of recent research discoveries and discuss the current gaps in knowledge. This session highlighted the crucial need for increased communication, care, and collaboration between researchers, physicians, biotech and pharma professionals, and individuals with TSC and their family members to fuel future scientific breakthroughs and continue to improve the quality of life for individuals impacted by TSC.

The keynote address was presented by **Martina Bebin, MD, MPA,** from the University of Alabama at Birmingham. Dr. Bebin currently serves as the co-director of the UAB TSC Clinic and has over 20 years of experience studying clinical epilepsy and TSC. She is an original member of the TSC Clinical Research Consortium and has directed numerous NIH-funded TSC clinical research efforts. Her keynote address recapped the outcomes and impact of the Preventing Epilepsy using Vigabatrin in infants with TSC (PREVeNT) Trial (DOI: 10.1002/ana.26778). The PREVeNT trial was a Phase IIb clinical trial that tested whether early vigabatrin treatment delayed epilepsy onset and improved neurocognitive outcome in TSC infants. Overall, preventative treatment with vigabatrin did not significantly improve neurocognitive outcome or lower the incidence of focal seizures compared to participants who were closely monitored and began treatment with vigabatrin when seizures began. There was an association with a lower incidence of infantile spasms in the vigabatrin preventative treatment group. Further data analysis is underway to dig deeper into the rich data set generated from this study. A new Phase II clinical trial, TSC-STEPS, is underway to determine the safety and efficacy of early sirolimus (also known as rapamycin) treatment to prevent or delay seizure onset in TSC infants. Overall, clinicians and researchers agree that a consensus statement needs to be released to address current medical recommendations and preventative treatment strategies for epilepsy.

At the opening night dinner **Anna Jansen, MD, PhD,** was presented with the Manuel R. Gomez Award in recognition of her extraordinary scientific and humanitarian efforts to find a cure for TSC while improving the lives of those affected. Her work has significantly impacted the field of TSC research and led to the first dedicated funding for a grant on TAND. Additionally, 18 early career researchers were recognized with the Vicky H. Whittemore Travel Award based on their outstanding abstract submissions. Importantly, 39% of these individuals were from groups historically underrepresented in biomedical research.

Early Career Researcher Symposium

Prior to the start of the main researcher conference, the Early Career Researcher (ECR) Symposium was held the morning of September 7th, 2023. This meeting served as a platform for early-stage career researchers, including graduate students, postdoctoral fellows and junior faculty, to network, present scientific findings, and engage in career talks with established faculty and physicians. There were 60 attendees spanning 30 institutions and 11 countries. The

ECR Co-Chairs, **Nicole McDonald, PhD,** and **Uchenna John Unachukwu, PhD,** gave opening remarks, followed by two sessions of short talks.

In the first session, **Jerome Arceneaux, BS,** discussed how imaging mass cytometry, a multiplex antibody-based technique, was used to analyze the cellular composition of resected brain tissue from TSC patients. A distinct population of diagnostic cells was identified called "balloon cells." Balloon cells express progenitor markers and aberrant mTOR signaling markers. A deepened understanding of the cellular composition within TSC tissue has the potential to identify unique molecular markers and therapeutic targets against TSC.

Francesco Avanzi, presented data on the role of the S6 kinase (S6K), a downstream mTOR-effector, in TSC-related epilepsy. Deletion of *S6K* in TSC knockout mice significantly reduces the number of seizures. Phosphoproteomic analysis of the brain cortex revealed TREK-1, a potassium channel, is a potential downstream target of S6K. Phosphorylation of TREK-1 by S6K occurs in a rapamycin-dependent manner and could provide a novel mechanism for epilepsy development in TSC patients.

Marie Girodengo, MSCi, reported findings from a phosphoproteomic screen used to identify new targets of the mTORC1 kinase complex. Brain tissue from *Tsc1* conditional knockout mice and control mice was analyzed and differentially phosphorylated sites identified. Downstream analysis identified 25 novel mTOR targets, which had known roles in transcription, ubiquitination, chromatin remodeling, and calcium signaling. Importantly, several of these targets have known roles in neurodevelopmental disorders and could provide key insight into novel molecular mechanisms underlying the neurological manifestations of TSC.

Laís Cardozo, MSc, described results from a prospective study on TSC patients from Brazil with the aims to 1) identify the prevalence of TAND signs and 2) identify correlations with clinical history and neuropsychiatric characteristics. An intelligence assessment based on the TAND checklist was performed in 44 participants and clinical history evaluated. Overall, there was a high frequency of TAND manifestations and neurophysiological difficulties including difficulties in executive functions, dual-tasking, paying attention/concentrating and neuropsychological attention. These data support that a high frequency of TAND manifestations are associated with neuropsychological difficulties.

In the second session, **Apoorva Kasetti, MS, BPharm,** discussed the role of extracellular vesicles (EVs) in LAM progression. EVs were isolated from vehicle and everolimus treated patient-derived LAM cells. Compared to vehicle, EVs derived from everolimus treatment had increased integrin expression, cell migration proteins and cancer stem cell markers. Additionally, treatment with everolimus increased EV sphere size, migration and invasion. These results suggest that EVs secreted by everolimus treated LAM cells promote cancer stem-like phenotypes and may play an important role in LAM progression.

Kaushal Asrani, PhD, MBBS, presented findings on the role of AMPK, a conserved serine threonine kinase, in renal cells exhibiting loss of *Tsc1/2.* Increased AMPK activity and downstream substrate phosphorylation is observed in *Tsc2* knockout models *in vitro* and *in vivo*. AMPK activation drives nuclear localization of TFEB, an important transcription factor that controls multiple cellular processes. AMPK deletion decreases the growth of *Tsc2* knockout cells, suggesting that AMPK may be an important mediator of tumorigenesis in TSC.

Devin Barzallo, MSc, reported on the impacts of ultraviolet light on TSC skin tumors. A 27-person adult TSC cohort was analyzed to test the hypothesis that TSC skin tumors in sun-

exposed sites will have more UV mutations across the genome than sun protected sites. Biopsies obtained from TSC skin tumors were categorized based on expectation of sun exposure and whole genome sequencing performed. Results demonstrated that a greater number of mutations occurred in sun-exposed areas compared to sun protected areas, suggesting application of sunscreen may reduce mutational burden and skin disease in TSC.

Magdalena Losko, PhD, described studies exploring the mechanism by which *Tsc1* loss promotes bladder cancer development. RNA-sequencing analysis of a *TSC1*-mutated bladder cancer cohort compared to *TSC1* wildtype cohort demonstrated an enrichment of genes associated with mTORC1 signaling and lysosome activity in the mutated cohort. Out of 60 genes commonly upregulated in TSC tumors, 26 genes had overlap in the *TSC1* mutant bladder cancer cohort, including increased expression of TFE3. *TFE3* knockout in human *TSC1* mutant bladder cancer cells significantly reduced cell growth, suggesting TFE3 is an important transcriptional driver of *TSC1* mutated bladder cancer.

Following the short talks, a career-development panel took place featuring four distinct panelists: Dean J. Aguiar, PhD, Shafali Jeste, MD, Tracy King, MD, MPH, and Shui-Lin (Stan) Niu, PhD. This panel served as a platform to engage with early career researchers and discuss funding opportunities from the NIH and DOD as well as various career paths. These discussions emphasized the importance of young investigators to find great mentors who can guide them throughout their career path.

Chemical and Cell Biology

The first session of plenary talks described the molecular pathways altered in TSC and how these pathways can be exploited for the generation of new therapies. These findings spanned a wide variety of topics including the immune system, nutrient availability, RNA modifications, and extracellular vesicles, and how changes in these pathways contribute to the development of TSC, as discussed below.

Ziyang Zhang, PhD, discussed the development of a novel third generation mTOR inhibitor called RapaLink-1. RapaLink-1 combines the first and second generation mTOR inhibitors, rapamycin and Sapanisertib, respectively, using an inert chemical linker. Brain-specific inhibition of mTOR can be achieved by combining the brain-permeable RapaLink-1 mTOR inhibitor with a brain-impermeable competitive inhibitor, RapaBlock. The drug combination reduces off-tissue drug effects by mTOR inhibitors.

Katharina Maisel, PhD, presented on work investigating the hypothesis that immunotherapies can be repurposed in treating diseases other than cancer. Specifically, the use of toll-like receptor (TLR) agonists was tested as a way to overcome immunosuppression in LAM. Treatment with the TLR 9 agonist CpG enhances survival in a mouse model of LAM and reduces nodules in the lungs. Additionally, CpG treatment has a synergistic effect with rapamycin, and could serve as a new treatment option to treat LAM patients.

Ben Philpot, PhD, reported on the use of a high-throughput assay to identify novel therapeutics for a rare neurodevelopmental disorder termed Angelman Syndrome. Angelman syndrome is caused by deletions or mutations in the maternal *UBE3A* gene, as the paternal gene is usually silenced. A high-throughput imaging-based assay identified *Ube3a* unsilencers, including the topoisomerase inhibitor, Topotecan and a novel unsilencer termed UNCilencer53. These findings suggest small molecules can provide treatment for Angelman syndrome, although safety and efficacy studies still need to be performed.

Charilaos (Harry) Filippakis, PhD, described how macropinocytosis, a type of nutrient uptake designed to bring in extracellular nutrients, can serve as a metabolic vulnerability in TSC. Macropinocytosis is increased in TSC2-deficient cells, and Tryptophan serves as an essential amino acid that selectively stimulates macropinocytosis in TSC2-deficient cells. Inhibition of tryptophan metabolism using the SR-1 inhibitor selectively inhibits the proliferation of TSC2-deficient cells and has the potential to serve as a novel therapeutic treatment for TSC.

Joohwan Kim, PhD, discussed the role of RNA modification as a novel mechanism for rapamycin resistance in TSC tumor cells. N6-adenosine methylation (m6A) is a common mRNA modification that controls gene expression. Performing m6A RNA methylation sequencing identified 18 targets genes regulated by mTORC1, including MAPK13. Methylation of the MAPK13 kinase was found to reduce the efficacy of rapamycin. Treatment of rapamycin in conjunction with a MAPK13 inhibitor synergistically suppressed cell growth and proliferation of TSC patient-derived cells lines. These findings suggest MAPK13 could serve as a promising therapeutic target to sensitize cells to rapamycin.

Nicola Alesi, MD, PhD, presented on the role of the Transcription Factor EB (TFEB) in kidney tumorigenesis in TSC. In a mouse model with a kidney specific knockout of *Tfeb,* mice develop cystic kidney disease and have an increased kidney/body weight ratio. Double knockout of *Tsc2* and *Tfeb* normalizes the kidney phenotype and extends the mouse lifespan. Treatment of *Tsc2*-deficient cells with rapamycin led to increased TFEB phosphorylation and relocalization from the nucleus to the cytoplasm. Overall, these findings suggest TFEB may serve as an important therapeutic target for TSC.

David Ritter, MD, PhD, reported on the Stopping TSC Onset and Progression 2 (STOP2A) clinical trial which compared a precision dosing strategy to the conventional dosing strategy in TSC infants treated with mTOR inhibitors. Projected dosing recommendations were based on age, size and projected size of TSC infants and dose adjustments occurred every month. Using the precision dosing strategy, 100% of infants achieved target blood trough levels, while only 7 of the 13 infants on conventional dosing achieved target levels. Overall, the precision dosing strategy serves as a faster and more efficient way to achieve target blood trough levels in TSC infants. The STOP2B clinical trial is currently ongoing to refine this precision dosing strategy.

Ulrike Rehbein, PhD, MSc, BSc, described the role of Ras GTPase-activating protein-binding proteins (G3BPs) in mTORC1 signaling. G3BPs are primarily known as core components of stress granules, but preliminary data suggest G3BPs anchor the TSC complex to lysosomes, ultimately suppressing mTORC1 activation. Inhibition of G3BP1 in a zebrafish model disrupts neuronal activity and contributes to neuronal hyperactivity. Methyl-proteomics analysis identified G3BP1 is a target of the PRMT5 methylase, and methylation inhibits G3BP1-TSC2 binding and activates mTORC1 signaling. Targeting this signaling axis could serve as a novel way to increase the efficacy of current therapies.

Anil Kumar Kalvala, PhD, discussed the role of extracellular vesicles (EVs) is LAM progression. EVs were isolated from LAM patient-derived cells using ultracentrifugation and ultra-filtration techniques. EVs derived from *TSC2*-null cells promote the migration of patient-derived LAM cells through activation of the Integrin-beta-1-FAK axis. The *TSC2*-null EVs also increased cancer stem cell properties and metastatic potential of patient-derived LAM cells. These findings suggest EVs derived from *TSC*-null cells may play an important role in promoting lung colonization and LAM progression.

Biomarkers and Ethics in Early Intervention

The second plenary session discussed the use of biomarkers in the early detection of TSC and raised discussion on the ethics of early intervention. Topics also centered on early detection and intervention strategies for other neurodevelopmental disorders, including autism, and how these research findings translate to the TSC field.

Connie Kasari, PhD, presented research focused on early interventions for autism and how it applies to other neurological disorders, such as TSC. A modular intervention technique for autism, termed JASPER, targets developmental delays by layering multiple intervention methods. Importantly, parent mediated JASPER had significant positive effects on a child's social communication outcomes. The lessons that can be applied to treating TSC patients include applying early intervention techniques, using multiple intervention methods and adjusting interventions as needed.

Kate MacDuffie, PhD, MA, reported on the ethical considerations in early detection and intervention for children with autism. To accomplish this, parental motivations and attitudes on a hypothetical MRI test to predict autism in infancy were assessed. Most parents had a desire for diagnostic prediction, as it would provide more time to prepare prior to the onset of symptoms. Fewer parents wanted detailed predictions, as they were concerned about limiting expectations of their child's future abilities. Overall, these findings emphasize the importance of empowering parents to make their own medical decisions surrounding their children and providing them with the proper resources if they need.

Serguisz Józwiak, MD, PhD, described the results from the previously published EPISTOP clinical trial. EPISTOP was a long-term prospective study focused on comparing preventative versus conventional antiepileptic treatment in TSC infants. Overall, preventative treatment significantly delayed the onset of seizures and lowered the frequency of epilepsy compared to conventional treatment. These findings contrast the recently published PREVeNT trial, which showed no significant difference in preventive vigabatrin compared to placebo. Further discussion needs to occur to reconcile the differences in study outcomes. A follow-up study, called The ViRap project, is currently underway to compare the safety, tolerability and efficacy of Vigabatrin and rapamycin as a preventative treatment of epilepsy in infants with TSC.

Tanjala Gipson, MD, discussed early vocal development in infants with and without TSC and autism. Audio-video recordings of infants with and without autism were observed and analyzed for the use of sounds and syllables. Overall, TSC individuals had reduced babbling values compared to non-TSC individuals. Preliminary data suggests delays in vocal development were not significantly different between TSC individuals with and without autism, and future studies are warranted. An ongoing prospective study called BABY TALK is underway to characterize early vocal development in infants with TSC and predict developmental outcomes. If interested, please contact the study coordinator Lauren Davis (lauren.davis2@lebonheur.org) to get involved.

Jenny Do, MS, CGC, presented work focused on studying parental stress in TSC. To characterize the degree of parental stress and identify factors influential to parental stress, a comprehensive survey was drafted and distributed to 269 recruited parents to children with TSC. Overall, 50% of parents reported clinically relevant stress levels and would benefit from seeing a mental health professional. The most influential stressors were determined to be skin/ocular TSC features, seizure severity, and TAND diagnoses. This information can be leveraged to provide better support to parents in the clinical and direct them to the proper resources to alleviate parental stress in the future.

TAND (TSC-Associated Neuropsychiatric Disorders) and Epilepsy Research

The third plenary session centered on TSC-Associated Neuropsychiatric Disorders (TAND) and epilepsy research. This section of short talks described the outcomes of clinical trials as well as the development of future interdisciplinary projects to improve access to resources for individuals and family members impacted by TAND.

Nola Chambers, PhD, discussed the project outcomes and next steps for the TANDem Project, an international and multi-disciplinary project that seeks to empower families and indiviudals impacted by TSC through technology. The goals of the TANDem Project were to 1) develop an app that contains a quantifiable TAND checklist and consensus clinical guidelines to identify and treat TAND and 2) develop a global TAND consortium to promote networking between clinicians, researchers, individuals with TSC and their family members, and the general public. To accomplish these goals, TAND-SQ was developed and is currently being validated with the TSC Alliance and at Boston Children's Hospital, and a TAND toolkit with consensus recommendations and cluster specific recommendations can be found at: https://tandtoolkit.org/. Next steps include integrating this data into a mobile app that can be accessed worldwide.

Agnies van Eeghen, MD, PhD, described the design of the Epilepsy Comorbidities (EpiCom) trial, a decentralized ongoing phase 4 clinical trial. This study was designed to evaluate the behavioral outcomes associated with cannabidiol (CBD) treatment in people with TSC-associated seizures. Individuals that meet inclusion criteria must be between the ages of 1-65 years old, on at least one anti-seizures medication and exhibit moderate to severe behavioral challenges. Study endpoints include TAND outcomes, quality of life, seizure severity/outcomes, and the safety and tolerability of CBD. The trial is still enrolling patients and hopes to have the first results by 2026.

Michael Wong, MD, PhD, discussed the role of abnormal VEGF expression in the brain and its impact on cerebral vascular and the blood brain. VEGF is an important growth factor that promotes angiogenesis and modulates the proliferation and plasticity of neuronal cells. VEGF expression was increased in the cortex of a TSC mouse model and was blocked following treatment of rapamycin, an mTOR inhibitor. Additionally, these mice also exhibited increased angiogenesis, abnormal vascular structure and increased blood brain barrier permeability, which could be reversed using the VEGF receptor agonist, apatinib. Further investigation into these mechanisms is needed, but these results suggest targeting the VEGF pathway and modulating the blood brain barrier could have important therapeutic implications in TSC.

Martina Bebin, MD, MPA, presented on behalf of **Howard Weiner, MD**, on the impact of advances in neurosurgery in TSC. Improvements in surgery for children with TSC and epilepsy has grown within the last 25 years and could serve as an important medical option moving forward. Recent research efforts have focused on identifying the targets for potential surgery, including identifying the extent of the epileptogenic zone through MRI, SPECT, PET, MEG, EEG and electrode scans, as well as determining the functional status of the cortex. Case studies reveal that brain surgery for epilepsy can not only eliminate or reduce seizures, but also improve cognitive development and enhance quality of life. Further research will continue to refine medical guidelines and allow further expansion of medical treatments for individuals with TSC.

Organoids and Cell Development

The fourth session of plenary talks emphasized the importance of developing novel and more complex models to study TSC. The following talks describe the development of novel 3D

research models paired with innovative imaging techniques to better understand the complex cellular interactions in TSC.

Manoocher Soleimani, MD, reported on the mechanisms of renal cystogenesis and how it contributes to kidney cyst expansion in TSC. Transcriptomic analysis of kidney RNA comparing wildtype and *Tsc1*-knockout mice revealed multiple targets of cyst development, including Foxi1, CLC5 and H^+-ATPase subunits. Follow-up studies demonstrated Foxi1 is critical to cystogenesis in TSC. Deletion of *Foxi1* completely abolishes kidney cysts *in vivo* and inhibits mTORC1 activity. Overall, these studies reveal multiple potential therapeutic targets inf TSC renal cysts.

Tasnim Olatoke, discussed the important role of STAT1 in LAM pathogenesis. Single cell RNAseq analysis of LAM lung tissue identified a unique population of uterine-similar cells (LAM^{CORE}) that are absent in normal lung tissue. This cell population was enriched for genes associated with the HOX/PBX1 signaling axis. Network predication analysis revealed that STAT1 is a potential downstream target of PBX1. Inhibition of STAT1 using the chemotherapy Fludarabine induced apoptosis of *Tsc2*-null cells *in vitro.* Overall, these findings suggest that the HOX/PBX1 signaling axis promotes survival and lung colonization of TSC2-null cells, and targeting this pathway may restrict LAM progression.

Jennifer Sucre, MD, presented on early lung development and how it applies to TSC. Specifically, a novel 4D imaging technique was developed to view alveologenesis in precision cut lung slices and better understand spatial relationships during lung development. SOPi light sheet microscopy and mathematical modeling were used to track changes in cell shape and movement at a single-cell resolution. Analysis identified a mesenchymal ring structure by which epithelial cells extrude to form new alveoli. Treating cells with CHIR, a WNT activator, demonstrated increased cell motion and impaired alveologenesis. These findings identify a novel 4D platform that enables the analysis of cellular relationships and alterations at a single-cell resolution level that can be leveraged for analysis of other disease models.

Nina Corsini, PhD, described the development of a novel TSC organoid model to study network pathology and cerebral tumor development. Patient-derived cells from patients with known *TSC2* mutations were isolated and reprogrammed to iPSCs. Neuronal outgrowth was achieved using selection media and organoids generated. Single cell RNA-sequencing analysis of organoids identified a distinct neural stem cell type called caudal late interneuron progenitor (CLIP) cells. CLIP cells were enriched in tumors, had lower levels of *TSC2* and expressed EGFR. Treating organoids with various EGFR inhibitors led to a reduction in organoid size, suggesting a potential treatment for TSC.

Jeffrey Calhoun, PhD, reported on the use of a multimodal framework model to resolve variants of uncertain significance (VUS) in *TSC2.* VUS are single amino acid substitutions that lack enough data to be classified as pathogenic or benign. Using known benign and pathogenic mutations, a predictive modeling algorithm was built to predict the outcome of unknown VUS. The current model shows immense promise and classifies 93% of the VUS learning data correctly, with most unknown VUS predicted as benign. Functional characterization validates these findings through the generation of multiple *TSC2* variants. Although most variants look benign, one variant, p.Ala607Glu, was found to be likely pathogenic. Further validation of these predictive algorithms will enable the increased understanding of VUS and enable better prediction of TSC outcomes and treatment options.

Hot Topics Advancing TSC Research and Clinical Care

The final session of plenary talks discussed current hot topics in TSC research and clinical care. These topics include ongoing clinical trials, developing online research platforms, increasing diversity in clinical trials, and caring for TSC individuals who are pregnant or want to become pregnant.

A group of short presentations on ongoing clinical trials kicked off the final plenary session. **Andy Liu, MD, MS,** presented on the link between TSC and Alzheimer's Disease and how accumulation of pTau may lead to neuropsychological alterations. To test this, a two-year observational clinical trial is underway called TSART. TSART is actively recruiting, and participants will be assessed through the TAND checklist, neuropsychological testing, blood samples and genetic testing. **Annelieke Müller** discussed the development of the TSC patient-reported outcomes (TSC-PROM) study to determine the impact of TSC on quality of life. Reported outcomes include physical functioning, mental functioning, activities/participation and social support, and the study was validated using a multidisciplinary expert group and cognitive interview study. The goal of TSC-PROM is to expand to clinical trials to gain better insight into the experience of TSC adults in these settings. **Renata Lazarova, MD,** reported on an ongoing phase 2b clinical trial called GALENE to determine the safety and efficacy of basimglurant in seizure control. Basimglurant is an mGlu5 receptor inhibitor that reduces seizures in TSC knockout mice by reducing aberrant protein synthesis. The primary endpoint will assess seizure control in drug versus placebo arms. Finally, **Ian Miller, MD,** discussed an ongoing phase 3 clinical trial assessing the role of Ganaxolene as an anti-seizure medication. Criteria for enrollment include anyone 1 to 65 years of age who experiences eight or more seizures per month. Please visit www.trusttsctrial.com to enroll.

Joseph Bateman, PhD, shared the development of the UK Rare Disease Research Platform, which is a collaboration between the UK medical Research Council and National Institute for Health and Care Research. The goal of the platform is to coordinate and addresses challenges in UK rare disease by connecting researchers with existing investors, industry, patients and other researchers. Currently, there is a central hub with 11 coordinating nodes. One example is the mTOR pathway Diseases node, which is currently building a registry of patients and assembling a team to develop a non-invasive genetic testing technique to identify mTOR pathway disease. The overall goal of these hubs to aid in the progression of science projects that will benefit the international TSC research community and promote collaboration.

Isaac Rodriguez-Chavez, PhD, PHS, discussed the importance of increasing diversity in clinical research trials to improve outcomes for rare diseases. Specifically, of the 98 current ongoing clinical trials for TSC, almost all are centralized and exclusive, which excludes a large amount of individuals. The COVID-19 pandemic demonstrated the ability to implement decentralized clinical trials and increase diversity within clinical trials. In order to accomplish this, access to technology and the use of digital solutions need to be implemented to improve clinical trial outreach and data collection.

Meredith Rose, MS, reported on pregnancy risks in adult patients with TSC. There is a critical unmet need to create pregnancy management guidelines for adults with TSC. To assess current recommendations and guidelines, a descriptive cross-sectional survey was administered through REDCaP to 87 health care providers. Over 63% of providers considered a patient with TSC a "high-risk" pregnancy even with no clinically significant TSC manifestations. Almost every provider recommended at least one additional clinical evaluation following pregnancy such as genetic counseling or pulmonary evaluation. There was limited provider consensus on the use

of mTOR inhibitors during pregnancy, thus emphasizing the need for further research and development of consensus guidelines moving forward to better care for pregnant TSC patients.

Breakout Working Groups:

Transition from Pediatric to Adults

Hosted by Jamie Capal, MD, and Elizabeth Thiele, MD, PhD, this breakout group discussed the challenging role of transitioning TSC patients from pediatric to adult care and what measures need to be implemented to aid this transition. Major challenges include the need to transition multiple organ systems and specialists, gender differences, and the reality that not every patient can be near a TSC center of excellence for care. Potential solutions included establishing care networks, promoting research initiatives in this area, collaborating with outsides groups including family navigators/social workers, and developing an educational program for individuals looking to know more about TSC.

Neurodevelopment and Early Intervention

Hosted by Shafali Spurling Jeste, MD, and Daniel Vogt, PhD, this breakout group focused on the need to better understand the underlying mechanisms driving neurodevelopment disorders. Discovering these mechanisms could lead to better biomarkers and treatment options for individuals with TSC. To address the source of heterogeneity in neurodevelopmental outcomes, discussions emphasized the need for a large-scale effort to better understand the nuances and differences in outcomes. One example was the divergence in developmental outcomes in twins with TSC. Additionally, discussions led to the suggestion of a large scale SMART design study that includes both medications and behavioral intervention to better assess the right treatment for each individual child with TSC.

Cellular Energetics and Metabolism

Hosted by Oded Volovelsky, MD, PhD, and Gina Lee, PhD, discussions in this breakout group centered on exploiting metabolic changes within TSC to develop novel therapeutic treatments and improve disease management. There was a general consensus that there is a potential to use metabolic and nutritional supplementations to overcome certain limitations, such as rapamycin treatment. Additionally, although prior studies have focused on investigating anabolic pathways, there was an emphasis on the need to study catabolic pathways in the future. One example is increased lysine breakdown observed in TSC cells. Thus, these metabolic differences could serve as a powerful therapeutic tool in the future.

Big Data and Single Cell Approaches/Analysis

Hosted by Rebecca Ihrie, PhD, and Laura Farach, MD, this breakout group discussed the importance of big data in advancing TSC research, while also highlighting the key challenges. Suggestions to improve collaboration and progress in big data research included making a centralized TSC-focused directory where researchers can view different datasets previously generated and view contact information for principal investigators. Another suggestion was to host a working group to define common data terms and definitions to ensure data analysis is consistent across disciplines and research groups. There was also a desire to create online portals and assemble data repositions to accrue data from TSC patients around the world. This would enable the generation of more robust research studies in the future. Lastly, the ability to offer consulting on study design prior to starting research studies was suggested to ensure data sets are generated in a meaningful land consistent way.

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