



2021 Virtual International TSC & LAM Research Conference Attendees Focus on “Driving Discoveries Beyond Boundaries”

The *2021 Virtual International TSC & LAM Research Conference: Driving Discoveries Beyond Boundaries* held October 28-30, 2021, welcomed 179 people from 18 countries. Co-sponsored by the TSC Alliance® and The LAM Foundation, the conference featured three plenary sessions with 17 oral presentations and two poster sessions with 14 posters. Additionally, two half-day sessions of “topic-based discussion” brought together clinical and basic science researchers to discuss cross-cutting topics, including big data and clinical translation.

The keynote address was delivered by Daphne Koller, PhD, Founder and CEO of Insitro, Inc. Dr. Koller is best known for her work as a pioneer in the artificial intelligence (AI) field and as a thought leader in precise, targeted medicine. Her talk, “Transforming drug delivery using digital biology,” introduced the concept of machine learning as an approach to drug discovery and development. Dr. Koller’s talk highlighted the benefits of machine learning for rare disorders like TSC, as biological data (MRI scans, pathology data, genetics) comprise massive datasets that are uninterpretable by humans because of their scale. While humans have a difficult time parsing these integrated datasets, computers can interpret subtle, previously unknown drivers of disease that might prove to be useful therapeutic targets.

This article summarizes a selected subset of presentations, and we regret not all talks and posters could be described in this overview.

Discovering New Ideas for Therapeutic Targets and Human Cell-Based Models

Conference plenary sessions began with Kathrin Thedieck, PhD, whose lab at the University of Innsbruck (Austria) has been studying a protein crucial to understanding the similarities between cells lacking functional TSC proteins and normal cells reacting to external stress stimuli. This protein—G3BP—plays a role in the TSC-mTOR signaling cascade; it helps the TSC protein complex tether to lysosomal proteins so that it is in the proper position to inactivate mTOR.

Dr. Vivi Heine and her lab at Amsterdam UMC have been studying human-derived samples and creating induced pluripotent stem cells (iPSCs) to examine neuronal activity. This research has shown that it is possible to recapitulate TSC-associated phenotypes in cell-based models. This is

important for understanding human disease biology and testing possible new drugs on cells derived directly from people with TSC.

Dr. Helen Bateup presented her work using organoids, which are three-dimensional assemblies of iPSC-derived cells composed of a mixture of the different types of cells found in the brain, to understand the early -developmental changes that lead to the formation of cortical tubers. Dr. Bateup's work shows how dysregulation of mTOR signaling during early cortical development contributes to altered cellular differentiation and ultimately, the formation of tubers.

Predicting and Preventing Manifestations of TSC and LAM

Dr. Simon Johnson shared data from a retrospective analysis that utilized machine learning to examine LAM patient records and biospecimens. The methods discussed by Dr. Johnson could be used to potentially stratify care for individuals at risk for developing LAM, reduce uncertainty in predicting disease severity, and improve overall outcomes.

Dr. Jamie Capal described predictors of autism from the TSC Autism Center of Excellence Research Network (TACERN) clinical study. Dr. Capal shared data that showed a correlation between seizure burden and developmental outcomes. These data, in tandem with other studies of early development and seizure onset, have provided a foundation for several clinical studies, including the currently enrolling TSC-STEPS trial (NCT04595513).

Breakout Discussion Groups

Conference attendees were invited to join afternoon topic-based discussion sessions on Thursday and Friday of the conference week. Conference Co-Chairs Dr. Rebecca Ihrle and Dr. Nishant Gupta moderated the panel discussion on Thursday and Friday, respectively. Following panel presentation and group Q&A, attendees were randomly assigned to breakout rooms hosted by panelists to discuss the topics on a deeper level and ensure all attendees had an opportunity to engage in small-group discussions.

Extracting meaning from multi-omics datasets

Presentations by Drs. Ihrle, Krymskaya, Xu, and Davis focused on many different aspects of big data – ranging from introducing new tools that researchers might find useful in their analyses, sharing datasets and open science, and validating results using patient samples. Breakout discussions following these presentations focused on the need for a centralized repository of datasets specific to TSC and LAM researchers. Participants also suggested single-day workshops to teach researchers how to use and analyze big data, which would not only contribute to accelerating research but also would help develop early career researchers' skills in an accessible, practical way.

Informing and enabling clinical trials, from bench to randomized clinical trials

Conference attendees heard presentations from Drs. Aguiar, Henske, and Ess focusing on the current resources available to investigators who are interested in translating their findings from bench to bedside. Dr. Ajamete "Aj" Kaykas from Insitro joined for the panel discussion and

Q&A, which centered on uncovering some of the general barriers to translation researchers are facing. Breakout discussions focused on how the TSC Alliance and the LAM Foundation may assist researchers in navigating the complicated translation process, including potentially funding high-risk, high-reward biomarker studies, improving clinical trial designs, and prioritizing the use of existing data (e.g., from the TSC Natural History Database) for longitudinal projects.

Early-Career Researcher Symposium

To close the conference, co-chairs Charilaos “Harry” Filippakis, PhD and Gerta Hoxhaj, PhD developed an engaging and practical Early-Career Researcher Symposium. This meeting brought together a Career Development Panel (Rebecca Ihrle, PhD; Mark Keezer, MD, PhD; Gina Lee, PhD; Dario Lemos, PhD; and Alexander Valvezan, PhD) to provide guidance and advice to researchers who are early in their trajectories – be it academia, industry, advocacy, or anything in between. Drs. Filippakis and Hoxhaj also invited early-career researchers who submitted abstracts to present and receive feedback on their oral presentations.

Acknowledgments

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