Boston Children's Hospital

# a child thanks you

ROSAMUND STONE ZANDER TRANSLATIONAL NEUROSCIENCE CENTER

Boston Children's Hospital

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

# Driving patient-centered research and care forward

A report on the Rosamund Stone Zander Translational Neuroscience Center

December 2021

## A message from Dr. Kevin Churchwell

Many believe that "if you want to go fast, go alone; but if you want to go far, go together."

However, the transformative gift you made to realize Dr. Mustafa Sahin's vision shows that you, like him, recognize that this proverb is actually only half true. The world needs us to enlist many disciplines to work together if we want to go far *and* move fast to make a difference for children and families facing challenging pediatric nervous system disorders.

At the Rosamund Stone Zander Translational Neuroscience Center, we are bringing together researchers with deep expertise and promising young talent with fresh ideas, from across many medical, scientific and technology fields. Your gift allows Boston Children's Hospital to unite the world's brightest minds to drive advances in early detection and treatments for children with neurological and neurodevelopmental disorders.

By removing traditional barriers between clinicians and scientists, we can:

- make more rapid, genome-based diagnoses.
- develop more effective, precisely targeted drugs and therapies.
- create specialized clinical care programs, coordinated across disciplines.

And thanks to your overwhelming generosity, we are optimally positioned to travel both far and fast along Dr. Sahin's ambitious roadmap.

Your support has given Boston Children's the freedom to pursue what's truly important for patients, both the infants and kids receiving treatment in Boston and the countless children around the globe who benefit from the breakthroughs made here. Care for individuals with neurodevelopmental disorders is what drives research at the center–and vice versa. We no longer have to wait on the National Institutes of Health or the pharmaceutical industry to bring brighter futures to children and families facing brain disorders.

With deep appreciation,

**Kevin B. Churchwell, MD**
President and CEO, Boston Children's Hospital

## One Transformative Gift. Limitless Possibilities

Autism spectrum disorder (ASD). Hearing loss. Down syndrome. Catastrophic seizures. Neurodevelopmental disorders so common that you likely know someone with one… and others so rare that the parents of affected children may never meet another soul who understands what they're going through.

What these disorders of the brain and nervous system have in common is that all the children they touch deserve medical answers that help them enjoy a healthy and happy life. Thanks to your clear-eyed view of what's possible when clinicians and scientists are free to conduct research across disciplines, without boundaries, the sky is the limit when it comes to Boston Children's solving even the world's most challenging medical problems.

The impact of your gift on the lives of infants, adolescents and teens across the world surely will be incalculable. But here's how the Rosamund Stone Zander Translational Neuroscience Center (RSZ TNC) worked to revolutionize diagnostics, care and family support in year one—from discovering important genes, to developing zebrafish models, to uniting the best minds and purest passion from inside and outside pediatric medicine to make a difference.

## Traveling farther—and faster—on the wheel of discovery

Finding answers for children with rare neurodevelopmental disorders can be a trying journey for those who love them. Often a definitive diagnosis and a clear understanding of what a condition means for a child's long-term health and unfolding mind—never mind an effective treatment—evade affected families for years.

RSZ TNC's Dr. Chopra (far right) and Siddharth Srivastava, MD (far left) with a family participating in a new multidisciplinary specialty clinic for patients with Kleefstra Syndrome. Read more on page 9.

Someone who knows this all too well is Maya Chopra, MBBS, FRACP, director of translational genomic medicine at the RSZ TNC, who joined the team in May 2020.

In her previous position at the Imagine Institut des Maladies Génétiques in Paris, Dr. Chopra conducted research under the mentorship of Professor Jeanne Amiel, seeking to identify new diagnoses in children with head and facial differences. During the course of this work, Dr. Chopra and Professor

Amiel saw a teenage girl with severe developmental delays, epilepsy, absent speech, recurrent infections and unusual facial features. The patient had seen many doctors and undergone numerous investigations over the years, but the genetic basis of her condition remained unknown.

Dr. Chopra and her colleague Christopher Gordon, PhD, analyzed all the girl's coding genes and noted a rare variant in a gene called ANKRD17. At the time, scientists knew very little about this gene. But over the next four years, Dr. Chopra connected with international colleagues who also had patients with rare ANKRD17 variants. Together, these researchers built a picture of a new, previously unrecognized genetic syndrome. The *American Journal of Human Genetics* published the collaborative gene discovery study earlier this year, and OMIM (a database of genes and genetic conditions) named the rare disorder "Chopra-Amiel-Gordon syndrome," or CAGS, after Dr. Chopra and her collaborators.

Now, Dr. Chopra and her fellow Boston Children's researchers are harnessing the revolutionary infrastructure of the new RSZ TNC and a $300,000 pilot project grant to better understand and treat this syndrome.

Dr. Chopra will work with a new group of children with this disorder to create a fuller portrait of the genetic, neurobehavioral, clinical and imaging spectrum clinicians see with CAGS. Meanwhile, Elizabeth Buttermore, PhD, the newly appointed director of translational in vitro models at the RSZ TNC, will use patient skin and blood samples to create and describe neurons specific to individuals with CAGS. This work will allow us to rapidly screen potential therapies. Conducting this preclinical research in parallel with the clinical effort to understand the syndrome allows our researchers to move more quickly from discovering genes to exploring potential treatments.

The CAGS research is one of five pilot projects funded (see page 7) in the RSZ TNC's first year. And it's just one example of the progress bench, preclinical and clinical researchers can make when they inform each other's efforts in real time.

Historically, dollars available from the National Institutes of Health and other funding sources steer research on pediatric nervous system disorder treatment, explains Rosamund Stone Zander Chair Mustafa Sahin, MD, PhD, the director of the RSZ TNC.

"The creation of the center allows *us* to be the engine generating ideas and research to help children with rare disorders that haven't yet been described, versus just being reactive to available funding," Dr. Sahin says.

## Growing our faculty research engine

By establishing the RSZ TNC, you've allowed Dr. Sahin to attract the very best minds. Together, they can realize the future of personalized medicine for children with neurological and neurodevelopmental disorders.

Proof exists that gene therapy can effectively treat a neurological disorder, notes Dr. Sahin. Boston Children's is one of the first pediatric hospitals in the nation to offer an FDA-approved gene therapy to treat spinal muscular atrophy (SMA). The treatment, which clinicians administer via a vein in a single hour-long procedure, prevents further motor neuron and muscle degeneration by replacing the defective or missing gene that causes SMA.

However, "while we have a very active gene therapy program, we don't have a lot of expertise in addressing brain disorders with gene therapy," Dr. Sahin says. So, at the recommendation of its external advisory board, the RSZ TNC has decided to pursue "young talent who will adapt to changes in this very fast-growing area and become leaders of new technologies being developed."

The first such rising star is Ranjan Batra, PhD, who has accepted an offer to join the team as an assistant professor, starting in early 2023.

Dr. Batra is currently the vice president of research and development at Locanabio Inc. in San Diego, where he's trialing several cutting-edge interdisciplinary approaches to RNA targeting. He also serves as the lead investigator on research to develop an RNA-targeting gene therapy funded by the Muscular Dystrophy Association. At Boston Children's, Dr. Batra plans to establish a translational research program for gene therapy to treat neuromuscular and neurological disorders, including Duchenne muscular dystrophy and Dravet syndrome, a rare but catastrophic form of lifelong epilepsy.

This girl received a new FDA-approved gene therapy to treat spinal muscular atrophy at Boston Children's. The RSZ TNC seeks to develop other gene therapies for brain disorders.

The center also extended an offer, now under negotiation, to an investigator with expertise in developing DNA-targeting gene editing therapies. Boston Children's will match $1 million in faculty lab startup costs for both faculty members and provide newly renovated lab space.

## Developing the drugs that our patients need most

In addition to recruiting experts to create new gene therapies for brain disorders right here at Boston Children's, your gift is allowing us to bring in new expertise in medicinal chemistry and additional expertise in translational genomics.

Boston Children's researchers often identify promising drug compounds for childhood neurological and developmental disorders through their state-of-the-art studies using human neurons, Dr. Sahin says. However, turning those discoveries into medicines that clinicians can give at the bedside typically requires pharmaceutical companies that share the same interest in developing the prototype drugs. Those partners can be especially challenging to find when a condition is rare.


By allowing us to recruit a medicinal chemist, your gift will help Boston Children's develop and trial new drugs without a pharmaceutical company with a vested interest.

Recruiting a medicinal chemist will give us the internal ability to develop and refine medicines, Dr. Sahin says. As a result, we can more quickly trial new compounds that patients desperately need—regardless of whether a company is vested in seeing those drugs succeed.

"We want to make better compounds that could be clinically useful," says Dr. Sahin, "and we also want to be able to improve on those compounds ourselves so we can accelerate that next level of translational medicine."

The recently established Translational Genomics Unit has rapidly become central to the mission of the RSZ TNC and its multidisciplinary research projects. The center is hiring a translational genomics specialist as well as an assistant professor to spearhead future projects.

The team has identified strong candidates for both faculty positions, planned for spring 2022 start dates.

## Thinking big about what we can change for children

In addition to the CAGS research mentioned earlier, four other multidisciplinary teams received one-year $100,000 pilot grants to advance their research in 2021. The breadth of these studies and their potential to change lives show the limitless possibilities that you have created.

### Exploring promising treatments for a rare disorder

Maxwell G. Heiman, PhD, and Olaf Bodamer, MD, PhD, will use their grant to work on a drug for treating Kabuki syndrome, a rare congenital disorder that causes intellectual disability and growth problems and can affect many other body systems. The researchers from the Division of Genetics and Genomics will use patient sample repositories and innovative animal models to screen a collection of 10,000 drugs to identify those that improve Kabuki syndrome symptoms.

Research to develop a gene therapy for a common type of childhood hearing loss for children such as Milea is just one of several life-changing endeavors being funded by RSZ TNC pilot project grants.

### Curing genetic hearing loss

Jeffrey R. Holt, PhD, and Olga Shubina-Oleinik, PhD, from the F.M. Kirby Neurobiology Center, will use their grant to investigate a treatment for patients with a genetic form of hearing loss. They seek to test novel methods to repair the large STRC gene—a common cause of hereditary hearing loss—using human inner ear cells generated from stem cells. If successful, their approach would offer a broad clinical window of opportunity to restore hearing, with intervention possible in babyhood, during the teen years or even later.

### Safeguarding the developing brain in utero

To help doctors around the world better care for babies diagnosed with heart disease in utero, Camilo Jaimes, MD, from the Department of Radiology, will use his grant to advance the use of a diagnostic tool called diffusion MRI, which reveals the random movement of water molecules in tissue. Dr. Jaimes will analyze a vast bank of MRI images of the brains of fetuses with heart disease. He aims to create an accessible way to catch important microscopic abnormalities in prenatal brain development, so clinicians can improve treatments for these vulnerable babies both before and after they're born.

### Providing more personalized care for children with Fragile X

Fragile X syndrome, the most common inherited genetic cause of intellectual disability, varies widely by patient when it comes to the degree of impairment. Carol L. Wilkinson, MD, PhD, from the Division of Developmental Medicine, and Nicole Baumer, MD, MEd, from the Department of Neurology, will use their grant to hopefully help doctors and families understand how Fragile X syndrome will affect each child's cognitive and language abilities. The researchers will compare electroencephalography (EEG) data in children with Down syndrome, typically developing children and children with Fragile X. By identifying prognostic EEG markers, Drs. Wilkinson and Baumer seek to create more personalized behavioral and medication therapies for individuals with Fragile X.

All five RSZ TNC pilot grant awardees began their funded projects in October 2021 and will have the opportunity to apply for a second year of funding. The center will award pilot grants annually totaling up to $750,000 per year.

## Setting the course for a new generation of leaders

Unlocking new possibilities for diagnosing and treating childhood brain disorders requires that we harness the potential of young scientists fluent in new technologies not widely used in medicine. To that end, the RSZ TNC has awarded the first two translational neuroscience fellowships to Wenkang "Winko" An, PhD, and Kristina Johnson, PhD.

Two new RSZ TNC fellows are bringing their expertise from outside pediatric medicine to improve diagnostics and care for patients with autism spectrum disorders, such as Nick.

"Both fellows come from fields outside pediatric medicine and from families that have children with neurodevelopmental disorders," say Dr. Sahin. "The new fellowships allowed us to attract their considerable talents to work with us, matching their broad interests and expertise with our multidisciplinary translational research teams."

Dr. An recently completed his PhD in electrical and computer engineering at Carnegie Mellon University, where he trained as an electrical and biomedical engineer specializing in signal processing, machine learning and noninvasive neuroimaging methods. Under the mentorship of Drs. Charles Nelson and Carol Wilkinson from the Laboratories for Cognitive Neuroscience in the Department of Developmental Medicine, he will focus on using advanced EEG to map early brain signals of language and communication difficulties in infants and toddlers. The research aims to create a screening method to dramatically

lower the average age of an ASD diagnosis, allowing for earlier interventions. Ultimately, Dr. An seeks to draw on engineering concepts to develop new diagnostics and treatments for individuals with neurodevelopmental disorders.

Dr. Johnson finished her PhD in the MIT Media Lab, where she worked at the intersection of neuroscience, engineering, and autism, using multidisciplinary techniques ranging from deep brain stimulation and fMRI neuroimaging to wearable biosensors and human-centered artificial intelligence systems. Under Dr. Sahin's mentorship, she will focus on understanding how rare genetic variation leads to neurodevelopmental phenotypes. Connecting the dots between these discoveries will allow clinicians around the world to more effectively diagnose and treat children with rare genetic syndromes that cause ASD and intellectual disability. Her long-term goal is to improve the lives of individuals with complex neurodevelopmental differences, especially those who have few spoken words, genetic disorders or intellectual disabilities.

The RSZ TNC will recruit new fellows annually and mentor them into translational neuroscience positions within academia, clinical care, and industry.

## Rallying the world to tap our collective strengths

Like Dr. Sahin, you understand that we must activate the limitless potential of everyone who cares about a rare genetic condition or pediatric neurological condition. To that end, we tapped your gift to support the RSZ TNC's collaborative work with patient advocacy groups.

One of the families finding hope from RSZ TNC research on AP4-related hereditary spastic paraplegia.

In February 2021, we partnered with iDefine—a U.S.-based organization dedicated to discovering life-changing treatments for those with intellectual disabilities stemming from genetic disorders—to convene the first International Kleefstra Syndrome Family & Scientific Conference. Patients, caregivers, doctors, and researchers gathered to discuss the latest research on this rare genetic condition, which impairs development and involves many body systems. With a grant from iDefine, Boston Children's created a new multidisciplinary specialty clinic for patients with Kleefstra Syndrome, led by Siddharth Srivastava, MD, in the Department of Neurology and Anne O'Donnell, MD, PhD, in the Division of Genetics and

Genomics. We are additionally working with the iDefine and international collaborators on new research studies, including a natural history study to determine best practices for treating the mental health challenges, such as psychosis and behavioral regression that can be associated with Kleefstra syndrome.

In October, we hosted the fifth annual meeting of scientific advisors for Cure AP4, a foundation created by families of children affected by AP4-related hereditary spastic paraplegia. This set of four extremely rare and debilitating neurodegenerative disorders has no known treatments, but we were able to provide reasons for hope. Darius Ebrahimi-Fakhari, MD, PhD, and his team at the RSZ TNC shared how they've identified promising small molecules that were functionally restorative in patient-derived cells. His team is now studying these compounds' mechanism of action to optimize them before moving into testing in a zebrafish model and, eventually, mice. Dr. Ebrahimi-Fakhari's global effort to monitor the effects and spectrum of this disorder and its progression also has yielded new discoveries, including a common diagnostic imaging signature in the brain and—in what comes as a great relief to families—evidence that, although affected children may experience a regression in motor skills, they do not necessarily undergo similar cognitive declines. The RSZ TNC is planning for future gene therapy trials to treat AP-4-related hereditary spastic paraplegia.

## Exploring all avenues to bring new forms of healing and renewal

Elsewhere on the world stage, a Swiss pharmaceutical company launched an international clinical trial to investigate a potential new therapy for seizures in tuberous sclerosis complex, a rare genetic condition that causes tumors to grow in the body. The drug under investigation by Noema Pharma is based on a study Dr. Sahin's lab published in 2017 showing that a particular group of compounds reduced seizures in a mouse model of tuberous sclerosis. Boston Children's will serve as a clinical trial site in 2022.

Also in 2021, Boston Children's conducted a trial of a potential treatment for a spectrum of complex neurodevelopmental disorders known as PTEN hamartoma tumor syndrome. The trial, which was initiated by Dr. Sahin and his collaborators through the NIH-funded Rare Diseases Clinical Research Network Developmental Synaptopathies Consortium, measured several cognitive and behavioral outcomes and EEG biomarkers. Kira Dies, a certified genetic counselor and the newly appointed executive director of the RSZ TNC, says that the initial data, which has been analyzed but not published yet, shows some potentially promising signals of treatment efficacy and lays the foundation for the next trial of the therapy.

Beginning in mid-2023, RSZ TNC affiliated researchers will have access to a newly built research suite of rooms in which to host clinical trial visits at the Boston Children's Brookline Brain, Mind & Behavior

Center. This sensory-friendly space will be more comfortable and convenient for participating children and families.

## The power of you

We are delighted to share this wonderful progress with you. In just one year, Boston Children's has used your transformative gift to:

- build the RSZ TNC leadership team needed to dismantle the traditional barriers to making, sharing and capitalizing on new discoveries across disciplines.
- usher in the future of targeted therapeutics, from new drugs to gene therapies, by assembling the talent and technology required to develop them at Boston Children's.
- seed critical research that will inform future clinical guidelines and provide a pipeline for clinical trials.
- unite an international talent pool to advance the science today—and attract and support the next generation of leaders who will create the cures of tomorrow.

Thanks to your belief in Dr. Sahin's vision and your willingness to take bold action, we are primed to make rapid and far-reaching progress in ensuring that every child with a rare or debilitating neurological condition has the chance for greater cognitive, mental, emotional, and physical well-being. Whether it is providing an answer as to which gene has impaired the development of a single child seen in Boston—or finding new treatments for the 1 in 100 children worldwide affected by an ASD—our work together gives these children and their families a chance at a more fulfilling life.

## Appendix: Publications by Mustafa Sahin, MD, PhD, 2020-2021

### Peer-reviewed scholarship in print or other media: research investigations

Behne R, Teinert J, Wimmer M, D'Amore A, Chen IP-F, Buttermore ED, Barrett L, Dwyer S, Chen T, Davies AK, Hirst J, Wiesener A, Segal D, Martinuzzi A, Duarte ST, Bennett JT, Bourinaris T, Houlden H, Roubertie A, Santorelli FM, Borner GHH, Robinson M, Lipton JO, **Sahin M**, Ebrahimi-Fakhari D. Adaptor Protein Complex 4 Deficiency: A Paradigm Of Childhood-Onset Hereditary Spastic Paraplegia Caused By Defective Protein Trafficking Hum Mol Genet Hum Mol Genet. 2020 Jan 15;29(2):320-334. doi: 10.1093/hmg/ddz310.

Schoenberger A, Capal JK, Ondracek A, Horn PS, Murray D, Byars AW, Pearson DA, Williams ME, Bebin M, Northrup H, Wu JY, **Sahin M**, Krueger DA. Language predictors of autism spectrum disorder in young children with tuberous sclerosis complex. Epilepsy Behav. 2020 Feb;103(Pt A):106844. doi: 10.1016/j.yebeh.2019.106844

Cook IA, Wilson AC, Peters JM, Goyal MN, E Bebin EM, Northrup H, Wu J, Krueger DA, Leuchter AF, **Sahin M**. EEG Spectral Features in Sleep of Autism Spectrum Disorders in Children with Tuberous Sclerosis Complex. J Autism Dev Disord 2020 Mar;50(3):916-923. doi.org/10.1007/s10803-019-04326-0.

Peters JM, Hyde, DE, Chu CJ, Boom M, Scherrer B, Madsen JR, Stone SS, Ouaalam H, Prabhu SP, **Sahin M**, and Warfield SK. Lesion-Constrained Electrical Source Imaging: A novel approach in epilepsy surgery for Tuberous Sclerosis Complex. J Clin Neurophysiol. 2020 Jan;37(1):79-86. doi: 10.1097/WNP.0000000000000615.

Karimi D, Peters JM, Ouaalam A, Prabhu SP, **Sahin M**, Krueger DA, Kolevzon A, Eng C, Warfield SK, Gholipour A. Learning to Detect Brain Lesions from Noisy Annotations. Proc IEEE Int Symp Biomed Imaging. 2020 Apr;2020:1910-1914. doi: 10.1109/isbi45749.2020.9098599.

Kodani A, Kenny C, Lai A, Gonzalez DM, Stronge E, Sejourne GM, Isacco L, Partlow JN, O'Donnell A, McWalter K, Byrne AB, Barkovich AJ, Yang E, Hill RS, Gawlinski P, Wiszniewski W, Cohen JS, Fatemi SA, Baranano KW, **Sahin M**, Vossler DG, Yuskaitis CJ, Walsh CA. Posterior Neocortex-Specific Regulation of Neuronal Migration by CEP85L Identifies Maternal Centriole-Dependent Activation of CDK5. Neuron. 2020 Apr 22;106(2):246-255.e6. doi: 10.1016/j.neuron.2020.01.030. Epub 2020 Feb 24. PubMed PMID: 32097629; PubMed Central PMCID: PMC7255387.

Bassell J, Srivastava S, Prohl AK, Scherrer B, Kapur K, Filip-Dhima R, Berry-Kravis E, Soorya L, Thurm A, Powell C, Bernstein JA, Buxbaum J, Kolevzon A, Warfield SK, **Sahin M** on behalf of Developmental

Synaptopathies Consortium. Diffusion Tensor Imaging Abnormalities in the Uncinate Fasciculus and Inferior Longitudinal Fasciculus in Phelan-McDermid Syndrome. Pediatr Neurol. 2020 May;106:24-31.doi: 10.1016/j.pediatrneurol.2020.01.006.

O'Brien AM, Bayet L, Riley K, Nelson CA, **Sahin M** and Modi ME. Auditory Processing of Speech and Tones in Children with Tuberous Sclerosis Complex. Front. Integr. Neurosci. 2020; 14. DOI=10.3389/fnint.2020.00014

Gergoudis K, Weinberg A, Templin J, Farmer C, Durkin A, Weissman J, Siper P, Foss-Feig J, Del Pilar Trelles M, Bernstein JA, Buxbaum JD, Berry-Kravis E, Powell CM, **Sahin M**, Soorya L, Thurm A, Kolevzon A. Psychometric Study of the Social Responsiveness Scale in Phelan-McDermid Syndrome. Autism Res. 2020 Aug;13(8):1383-1396. doi: 10.1002/aur.2299 PMID: 32406614.

D'Amore A, Tessa A, Naef V, Bassi MT, Citterio A, Romaniello R, Fichi G, Galatolo D, Mero S, Battini R, Bertocci G, Baldacci J, Sicca F, Gemignani F, Ricca I, Rubegni A, Hirst J, Marchese M, **Sahin M**, Ebrahimi-Fakhari D, Santorelli FM. Loss of *ap4s1* in zebrafish leads to neurodevelopmental defects resembling spastic paraplegia 52. Ann Clin Transl Neurol. 2020 Apr;7(4):584-589. doi: 10.1002/acn3.51018. PMID: 32216065.

Applequist J, Burroughs C, Ramirez A Jr, Merkel PA, Rothenberg ME, Trapnell B, Desnick RJ, **Sahin M**, Krischer JP. A novel approach to conducting clinical trials in the community setting: utilizing patient-driven platforms and social media to drive web-based patient recruitment. BMC Med Res Methodol. 2020 Mar 13;20(1):58. doi: 10.1186/s12874-020-00926-y. PMID: 32169041; PMCID: PMC7069058.

Grayson LE, Peters JM, McPherson T, Krueger DA, **Sahin M**, Wu JY, Northrup HA, Porter B, Cutter GR, O'Kelley SE, Krefting J, Stone SS, Madsen JR, Fallah A, Blount JP, Weiner HL, Bebin EM, on behalf of the TACERN Study Group. Pilot study of neurodevelopmental impact of early epilepsy surgery in tuberous sclerosis complex. Pediatr Neurol 2020 Aug;109:39-46. doi: 10.1016/j.pediatrneurol.2020.04.002. PMID: 32418847

Sánchez Fernández I, Yang E, Calvachi P, Amengual-Gual M, Wu JY, Krueger D, Northrup H, Bebin ME, **Sahin M**, Yu KH, Peters JM. Deep learning in rare disease. Detection of tubers in tuberous sclerosis complex. PLoS One. 2020;15(4):e0232376. doi: 10.1371/journal.pone.0232376. eCollection 2020. PubMed PMID: 32348367; PubMed Central PMCID: PMC7190137.

Di Nardo A, Lenoël I, Winden KD, Rühmkorf A, Modi ME, Barrett L, Ercan-Herbst E, Venugopal P, Behne R, Lopes CAM, Kleiman RJ, Bettencourt-Dias M, **Sahin M**. Phenotypic Screen with TSC-Deficient

Neurons Reveals Heat-Shock Machinery as a Druggable Pathway for mTORC1 and Reduced Cilia. Cell Rep. 2020 Jun 23;31(12):107780. doi: 10.1016/j.celrep.2020.107780. PubMed PMID: 32579942.

Frazier TW, Jaini R, Busch RM, WolfM, Sadler T, Klaas P, Hardan AY, Martinez-Agosto JA, **Sahin M**, PhD, Eng C on behalf of the Developmental Synaptopathies Consortium. Cross-Level Analysis of Molecular and Neurobehavioral Function in a Prospective Series of Patients with Germline Heterozygous *PTEN* Mutations with and without Autism. Mol Autism 2021 Jan 28;12(1):5.

Mariscal MG, Berry-Kravis E, Buxbaum JD, Ethridge LE, Filip-Dhima R, Foss-Feig JH, Kolevzon A, Modi ME, Mosconi MW, Nelson CA, Powell CM, Siper PM, Soorya L, Thaliath A, ThurmA, Zhang B, **SahinM** and Levin AR, on behalf of the Developmental Synaptopathies Consortium. Shifted Phase of EEG Cross-Frequency Coupling in Individuals with Phelan-McDermid Syndrome. Mol Autism. 2021 Apr 28;12(1):29. doi: 10.1186/s13229-020-00411-9.

Cohen AL, Mulder BP, Prohl AK, Soussand L, Davis P, Kroeck MR, McManus P, Gholipour A, Scherrer B, Bebin EM, Wu JY, Northrup H, Krueger DA, **Sahin M**, Warfield SK, Fox M, Peters JM; TACERN study group. Tuber locations associated with infantile spasms map to a common brain network. 2021 Apr;89(4):726-739. doi: 10.1002/ana.26015. PMID: 33410532.

Di Nardo A, Vasquez S, **Sahin M**. A Cell-Based Assay Optimized for High-Content Cilia Imaging with Primary Rat Hippocampal Neurons. STAR Protoc. 2020 Dec 3;1(3):100189. doi: 10.1016/j.xpro.2020.100189. eCollection 2020 Dec 18. PMID: 33377083

Uljarevic M, Frazier TW, Rached G, Busch RM, Klaas P, Srivastava S, Martinez-Agosto JA, **Sahin M**, Eng C, Hardan AY, Developmental Synaptopathies Consortium. Brief Report: Role of Parent-Reported Executive Functioning and Anxiety in Insistence on Sameness in Individuals with Germline PTEN Mutations. J Autism Dev Disord. (in press). DOI: 10.1007/s10803-021-04881-5

Hardan AY, Jo B, Frazier TW, Klaas P, Busch RM, Dies KA, Filip-Dhima R, Snow AV, Eng C, Hanna R, Zhang B, **Sahin M**. A randomized double-blind controlled trial of everolimus in individuals with *PTEN* mutations: Study design and statistical considerations. Contemp Clin Trials Commun. 2021 Feb 6;21:100733. doi: 10.1016/j.conctc.2021.100733

Ziegler M , Russell BE, Eberhardt K. Geisel G, D'Amore Angelica, **Sahin M**, Kornblum HI, Ebrahimi-Fakhari D. Blended Phenotype of Silver-Russell Syndrome and SPG50 Caused by Maternal Isodisomy of Chromosome. Neurol Genet. 2020 Dec 29;7(1):e544. doi: 10.1212/NXG.0000000000000544. eCollection 2021 Feb. PMID: 33553621

Chen PF, Chen T, Forman TE, Swanson AC, O'Kelly B, Dwyer SA, Buttermore ED, Kleiman R, Carrington SJS, Lavery DJ, Swanson LC, Olson HE, **Sahin M**. Generation and characterization of human induced pluripotent stem cells (iPSCs) from three male and three female patients with CDKL5 Deficiency Disorder (CDD). Stem Cell Res 2021 Mar 5;53:102276. doi: 10.1016/j.scr.2021.102276.

Anderson NC, Chen PF, Meganathan K, Afshar Saber W, Petersen AJ, Bhattacharyya A, Kroll KL, **Sahin M**, on behalf of the Cross-IDDRC Human Stem Cell Working Group5. Balancing Serendipity and Reproducibility: Pluripotent Stem Cells as Experimental Systems for Intellectual and Developmental Disorders. Stem Cell Reports. 2021 Jun 8;16(6):1446-1457. doi: 10.1016/j.stemcr.2021.03.025. Epub 2021 Apr 15.

Eberhardt K, Jumo H, D'Amore A, Alecu JE, Ziegler M, Afshar Saber W, **Sahin M**, Ebrahimi-Fakhari D. Generation and Characterization of Six Human Induced Pluripotent Stem Cell Lines (iPSC) From Three Families with *AP4M1*-associated Hereditary Spastic Paraplegia (SPG50). Stem Cell Res. 2021 May;53:102335. doi: 10.1016/j.scr.2021.102335

Giannikou K, Zhu Z, Kim J, Winden KD, Tyburczy ME, Marron D, Parker JS, Hebert Z, Bongaarts A, Taing L, Long HW, Pisano WV, Alexandrescu S, Godlewski B, Nellist M, Kotulska K, Jozwiak S, Roszkowski M, Mandera M, Thiele EA, Lidov H, Getz G, Devinsky O, Lawrence MS, Ligon KL, Ellison DW, **Sahin M**, Aronica E, Meredith DM, Kwiatkowski DJ. Subependymal giant cell astrocytomas are characterized by mTORC1 hyperactivation, a very low somatic mutation rate, and a unique gene expression profile. Mod Pathol. 2021 Feb;34(2):264-279. doi: 10.1038/s41379-020-00659-9

Yuskaitis CJ, Rossitto L, Groff KJ, Zhang B, Dhamne SC, Lalani LK, Singh AK, Rotenberg A, **Sahin M.** Factors influencing the acute pentylenetetrazole-induced seizure paradigm and a comprehensive review of the literature. Ann Clin Transl Neurol. 2021 Jul;8(7):1388-1397. doi: 10.1002/acn3.51375.

Jordan C, Geisel G, Alecu JE, Zhang B, **Sahin M**, Ebrahimi-Fakhari D. Disease Severity and Motor Impairment Correlate with Health-Related Quality of Life in AP-4-Associated Hereditary Spastic Paraplegia. Neurol Genet 2021 Jul 20;7(4):e605. doi: 10.1212/NXG.0000000000000605. eCollection 2021 Aug.

Sundberg M, Pinson H, Smith RS, Winden KD, Venugopal P, Tai DJC, Gusella JF, Talkowski ME, Walsh CA, Tegmark M, **Sahin M**. 16p11.2 deletion is associated with hyperactivation of human iPSC-derived dopaminergic neuron networks and is rescued by RHOA inhibition in vitro. Nat Commun. 2021 May 18;12(1):2897. doi: 10.1038/s41467-021-23113-z. PMCID: PMC8131375.

Steele M, Uljarević M, Rached G, Frazier TW, Phillips J, Libove RA, Busch RM, Klaas P, Martinez-Agosto JA, Eng C, **Sahin M**, Hardan AY on behalf of the Developmental Synaptopathies Consortium. Psychiatric Characteristics Across Individuals with PTEN Mutations. Front. Psychiatry - Child and Adolescent Psychiatry 2021 Aug 17;12:672070. PMID: 34489750 PMCID: PMC8418135 DOI: 10.3389/fpsyt.2021.672070.

Dalal J*, Winden KD*, Salussolia CL, Sundberg M, Singh A, Pham TT, Zhou P, Pu WT, Miller MT, **Sahin M**. Loss of Tsc1 in cerebellar Purkinje cells induces transcriptional and translation changes in FMRP target transcripts. eLife 2021 Jul 14;10:e67399. PMID: 34259631. PMCID: PMC8279760. DOI: 10.7554/eLife.67399

Uljarević M, Frazier TW, Rached G, Busch RM, Klaas P, Srivastava S, Martinez-Agosto JA, **Sahin M**, Eng C, Hardan AY, on behalf of the Developmental Synaptopathies Consortium. Towards better characterization of restricted and repetitive behaviors in individuals with germline heterozygous PTEN mutations. Am J Med Genet A 2021 Nov;185(11):3401-3410.
doi: 10.1002/ajmg.a.62458.

Ihnen SZ, Capal JK, Horn PS, Griffith M, **Sahin M**, Bebin EM, Wu JY, Northrup H, Krueger DA on behalf of the TACERN study group. Epilepsy is Heterogeneous in Early-Life Tuberous Sclerosis Complex. Pedi Neurol 2021 Jul 6;123:1-9. doi: 10.1016/j.pediatrneurol.2021.06.012

Ebrahimi-Fakhari D, Brechmann B, Ziegler M, Alecu JE, Eberhardt K, Jumo H, D'Amore A, Davies AK, Habibzadeh P, Faghihi M, De Bleecker J, Vuillaumier-Barrot S, Auvine S, Santorelli F, Neuser S, Popp B, Yang E, Barrett L, Hirst J, **Sahin M**. High-throughput Imaging of ATG9A Distribution in Fibroblasts as a Diagnostic Functional Assay for Adaptor Protein Complex 4 - Associated Hereditary Spastic Paraplegia.Brain Commun. 2021 Sep 25;3(4):fcab221. doi: 10.1093/braincomms/fcab221. eCollection 2021. PMID: 34729478

Di Nardo A, Rühmkorf A, Award P, Brennecke A, Fagiolini M, **Sahin M**. Phenotypic characterization of Cdkl5-knockdown neurons establishes elongated cilia as a functional assay for CDKL5 Deficiency Disorder. Neurosci Res. 2021 Oct 5;. doi: 10.1016/j.neures.2021.10.001. [Epub ahead of print] PubMed PMID: 34624412.

Capal JK, Williams ME, Pearson DA, Kissinger R, Horn PS, Murray D, Currans K, Kent B, Bebin EM, Northrup H, Wu JY, **Sahin M**, Krueger DA on behalf of the TACERN Study Group. Profile of Autism Spectrum Disorder in Tuberous Sclerosis Complex: Results from a longitudinal, prospective, multi-site study. Ann Neurol (in press).

Ebrahimi-Fakhari D, Alecu JE, Ziegler M, Geisel G, Jordan C, D'Amore A, Yeh RC, Akula SK, Saffari A, Prabhu SP, **Sahin M**, Yang E. Systematic Analysis of Brain MRI Findings in Adaptor Protein Complex 4-Associated Hereditary Spastic Paraplegia. Neurology. 2021 Sep 20;. doi: 10.1212/WNL.0000000000012836. [Epub ahead of print] PubMed PMID: 34544818.

Levy T, Foss-Feig JH, Betancur C, Siper PM, Pilar Trelles-Thorne M, Halpern D, Frank Y, Lozano R, Layton C, Britvan B, Bernstein JA, Buxbaum JD, Berry-Kravis E, Powell CM, Srivastava S, **Sahin M**, Soorya L, Thurm A, Kolevzon A. Strong evidence for genotype-phenotype correlations in Phelan-McDermid syndrome: Results from the developmental Synaptopathies consortium. Hum Mol Genet. 2021 Sep 24;. doi: 10.1093/hmg/ddab280. [Epub ahead of print] PubMed PMID: 34559195; NIHMSID:NIHMS1745180.

Hernandez JOR, Wang X, Vazquez-Segoviano M, Sobral-Reyes MF, Moran-Horowich A, Sundberg M, Lopez-Cantu DO, Probst CK, Ruiz-Esparza GU, Abdi R, Giannikou K, Henske E, Kwiatkowski DJ, **Sahin M**, and Lemos DR. A Tissue-Bioengineering Strategy for Modeling Rare Human Kidney Diseases In Vivo. Nat Commun. 2021 Nov 11;12(1):6496. doi: 10.1038/s41467-021-26596-y.

Srivastava S, Condy E, Carmody E, Filip-Dhima R, Kapur K, Bernstein JA, Berry-Kravis E, Powell CM, Soorya L, Thurm A, Buxbaum JD, **Sahin M**, Kolevzon A on behalf of Developmental Synaptopathies Consortium. Parent-Reported Measure of Repetitive Behavior in Phelan-McDermid Syndrome. J Neurodev Disord. 2021 Nov 5;13(1):53. doi: 10.1186/s11689-021-09398-7. PMID: 34740315.

Loureiro LO, Howe JL, Reuter M, Iaboni A, Calli K, Roshandel D, Pritisanac I, Moses A, Forman-Kay JD, Trost B, Zarrei M, Rennie O, Lau L, Marshall CR, Srivastava S, Godlewski B, Buttermore E, S**ahin M**, Hartley D, Frazier T, Vorstman J, Georgiades S, Lewis SME, Szatmari P, Bradley L, Anagnostou E, Scherer SW. A recurrent SHANK3 frameshift variant in Autism Spectrum Disorder. NPJ Genom Med. 2021 Nov 4;6(1):91. doi: 10.1038/s41525-021-00254-0. PMID: 34737294

de Vries PJ, Leclezio L, Gardner-Lubbe S, Krueger DA, **Sahin M**, Sparagana S, De Waele L, Jansen A. Multivariate data analysis identifies natural clusters of Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND). Orphanet J Rare Dis. 2021 Oct 24;16(1):447. doi: 10.1186/s13023-021-02076-w. PMID: 34689816

Mo A, Snyder LG, Babington O, Chung WK, **Sahin M**, and Srivastava S. Neurodevelopmental profile of HIVEP2-related disorder. Dev Med Child Neurol. 2021 Oct 26. doi: 10.1111/dmcn.15100. Online ahead of print. PMID: 34704275

Chen PJ, Hussmann JA, Yan J, Knipping F, Ravisankar P, Chen PF, Chen C, Nelson JW, Newby GA, **Sahin M**, Osborn MJ, Weissman JS, Adamson B, Liu DR. Enhanced prime editing systems by manipulating cellular determinants of editing outcomes. Cell. 2021 Oct 9:S0092-8674(21)01065-5. doi: 10.1016/j.cell.2021.09.018. Online ahead of print. PMID: 34653350.

Huang L, Bichsel C, Norris A, Thorpe J, Pevsner J, Alexandrescu S, Pinto A, Zurakowski D, Kleiman RJ, **Sahin M**, Greene AK, Joyce Bischoff J. Endothelial GNAQ p.R183Q Increases ANGPT2 (Angiopoietin-2) and Drives Formation of Enlarged Blood Vessels. Arterioscler Thromb Vasc Biol. 2021 Oct 21;ATVBAHA121316651. doi: 10.1161/ATVBAHA.121.316651. Online ahead of print.

## Other peer-reviewed scholarship

Constantino JN, **Sahin M,** Piven J, Rodgers R, Tschida J, for the Directors of the Intellectual and Developmental Disabilities Research Centers (IDDRC) Network. The Impact of COVID-19 on Individuals with Intellectual and Developmental Disabilities: Clinical and Scientific Priorities. Am J Psychiatry. 2020 Nov 1;177(11):1091-1093. doi: 10.1176/appi.ajp.2020.20060780.