CIVITAN BLURBS
2021

Dr. Matthew Alexander's lab has focused on identifying novel factors that regulate childhood neuromuscular disorders. In the past few years, we have identified a key microRNA pathway that drives Duchenne muscular dystrophy (DMD) pathogenesis and can be used as a biomarker for monitoring disease progression in clinical trials. We have also generated novel zebrafish models of limb girdle muscular dystrophy and other rare neuromuscular disorders and identified corrective drug molecules through drug screens. In the next few years, we have several projects focused on characterizing the role of the dystrophin gene (the main gene affected in DMD) in the brain to understand why 20-25% of DMD patients develop autism spectrum disorders (ASDs).

Hundreds of human studies have been conducted using external electrical brain stimulation, such as transcranial direct current stimulation (tDCS) for cognitive enhancement and amelioration of mental or behavioural dysfunction with little knowledge of the mechanism of its effects. Electrical brain stimulation has been used to enhance learning, to ameliorate a variety of cognitive or psychiatric disorders, such as depression, schizophrenia, substance abuse, dyslexia and Alzheimer's disease. However, there are little data about the mechanism of action of electrical brain stimulation. **Dr. Franklin Amthor** has been using the isolated mammalian retina to model electrical stimulation effects on the central nervous system, and also to model the mechanisms of neurodegenerative changes in the central nervous system. Unlike brain slices, a donor retina can be mounted for recording completely intact, and, light, the input that drives the retina, can be supplied in vitro in the isolated preparation, where subtle changes in the nervous system can be monitored.

Dr. David Bedwell is identifying small molecules that promote suppression of nonsense mutations found in a subset of patients with many genetic diseases. These compounds are being tested in a range of neurological disorders, including Rett Syndrome, CDKL5 Deficiency, FOXG1 Deficiency, and MPS I-H (Hurler Syndrome). These compounds act by restoring expression of the defective protein and may provide relief for patients carrying this class of mutation.

Dr. James Bibb is studying neuronal signal transduction and has identified mechanisms that mediate cognition and which control the integration of metabotropic and excitatory neurotransmission. Recently his group has discovered a novel systemic Cdk5 inhibitor which has neuroprotective, anti-depressive and anti-addictive properties. These studies may lead to new treatments to improve cognition and treat diseases including anxio-depressive, addiction, and head trauma disorders.

Dr. Waldemar Carlo is testing low-cost early developmental interventions to reduce neurodevelopmental impairment in at-risk infants in low- and middle-income countries. Birth asphyxia is the main cause of childhood developmental impairment worldwide. A multi-country randomized controlled trial led by UAB investigators showed that home-based, parent-provided early developmental intervention in children who survived birth asphyxia showed both cognitive and psychomotor improvements.

In a landmark study published this summer in *Nature* (Martinez-Garcia et al, 2020), **Dr. Scott Cruikshank** and colleagues focused on an area of the brain called the thalamic reticular nucleus - an area known for its role in childhood absence epilepsy. Cruikshank and colleagues demonstrated that sensory sectors of the thalamic reticular nucleus are each divided into two genetically, structurally and functionally

separate sub-circuits that process information in distinct ways that are consistent with the type of information they carry. Their study provides fundamental insights about how the flow of information to the neocortex is gated by specific inhibitory circuits in the thalamus. These fundamentals are necessary for understanding how the thalamic reticular nucleus may guide attention and potentially how attentional focus is diminished in diseases involving this nucleus (e.g., absence epilepsy).

Dr. Jeremy Day's lab has developed novel gene editing tools to understand how specific genes or groups of genes contribute the learning, memory, and neuropsychiatric disease. In the coming years, his lab will use this technology in animal models to study how genes that are dysregulated in diseases like drug addiction promote maladaptive cellular and behavioral phenotypes. In the future, this technology could also provide a way to reverse or ameliorate genetic deficits associated with neurodevelopmental, neurodegenerative, and neuropsychiatric disease.

There is currently an epidemic of myopia (nearsightedness), with some Asian countries having an incidence of myopia of about 90% and increasing rapidly in much of the rest of the world as well. Myopia does not just force people to wear glasses or contact lenses, a myopic eye is physically elongated, and this puts stress on the retina and is a major risk factor for sight-threatening diseases such as retinal detachment or macular degeneration. **Dr. Timothy Gawne**'s research is aimed at exploring the visual cues that the eye uses to regulate its growth during childhood, and is working on developing several different optical methods of preventing the development of myopia.

Dr. Matthew Goldberg has been studying drugs and other methods to enhance the function of PINK1, deficiency for which causes neurodegeneration similar to Parkinson's disease. Dr. Goldberg recently discovered that PINK1 normally functions not in neurons, but in other brain cells that protect neurons from various stresses. It is possible that drugs that activate PINK1 could provide neuroprotection and could be developed for preventing or treating neurodegenerative diseases.

Dr. Alecia Gross and her team have established a unique preclinical pipeline that can both rapidly identify candidate FDA-approved compounds in zebrafish models of retinitis pigmentosa (RP) and characterize the detailed mechanisms and optimize drug delivery in mouse RP models. There is a critical need for RP therapies. Work in with Gross Research Team addresses this fundamental need of how to delay retinal degenerations and retain visual function; slowing RD even 10% could greatly extend useful vision.

Within the Autism Spectrum Disorder Research Database Project at UAB Civitan-Sparks Clinics, **Dr. Kristi Guest** and Dr. Sarah O'Kelley are exploring the ASD phenotype in a clinical population. Current projects focus particularly on ASD clinical presentation among underrepresented groups, including rural populations, females, and individuals with rare genetic conditions (Pitt-Hopkins Syndrome, Tuberous Sclerosis Complex). Ongoing research in this area will elucidate patterns in clinical presentation across understudied groups, informing diagnostic practices, health care policy, and clinical care.

Dr. Anita Hjelmeland is testing new drugs and drug combinations to improve the treatment of brain tumors. Her laboratory studies a subgroup of stem cell-like brain tumor cells, also known as cancer stem cells, that can survive radio- and chemotherapy: they have identified treatments that decrease cancer stem cell survival. As cancer stem cells must be targeted to improve the survival of brain tumor patients, her research provides new opportunities for treatments that can be moved to the clinic.

Along with various associates, **Dr. Kejin Hu** collaborated on recent publications: 1. Quick, coordinated and authentic reprogramming of ribosome biogenesis during iPSC reprogramming. *Cells*. 9(11):2484; 2. Human transcription factors responsive to initial reprogramming predominantly undergo legitimate reprogramming during fibroblast conversion to iPSCs. *Scientific Reports* 10:19710; doi, 10.1038/s415989-020-76705-y; 3. Become competent in one day in preparation of boxplots and violin plots for novices without prior R experience. *Methods and Protocols*; 4. Profiling and quantification of pluripotency reprogramming reveal that WNT pathways and cell morphology have to be reprogramed extensively. *Heliyon*. 6(5):e04035. doi.org/10.1016/j.heliyon.2020.e04035; 5. A PIANO (Proper, Insufficient, Aberrant, and NO reprogramming) to the Yamanaka factors in the initial stages of human iPSC reprogramming. *International Journal of Molecular Sciences*, *21*(9), 3229; https://doi.org/10.3390/ijms21093229

Dr. David Knight's research is focused on better understanding the neural substrates of human learning, memory, and emotion using magnetic resonance imaging (MRI) techniques that include functional MRI, diffusion tensor imaging, and magnetic resonance spectroscopy. Studies from his lab have important implications for understanding healthy, as well as dysfunctional, emotion processes. Disruption of these processes plays an important role in the emotional dysfunction associated with mood, anxiety, and stress disorders. His recent work has centered on determining the impact childhood poverty, violence exposure, and substance use have on the neural circuitry that supports emotional function. This line of research will help identify neural processes that mediate susceptibility and resilience to stress, and offer insights into the development of emotion-related disorders.

Dr. Bruce Korf leads a national consortium conducting clinical trials for the group of neurodevelopmental and tumor predisposition disorders collectively called "neurofibromatosis." He has assembled a group that has modeled human *NF1* gene mutations is cellular and animal systems aimed at development of treatments that restore function to the mutated gene or gene product, effecting a mutation-guided precision therapy for NF1.

Dr. Adrienne Lahti has conducted a number of behavioral experiments that were pivotal in revealing the contribution of glutamate to the pathophysiology of schizophrenia. These studies demonstrated that ketamine, an N-methyl-D-aspartate (NMDA) antagonist, can mimic the symptoms and some of the phenotypic manifestations of schizophrenia. For the past 25 years, Dr. Lahti has used a number of imaging techniques to measure levels of brain glutamate and to study the relationship between glutamate and brain function in patients with schizophrenia. In collaboration with Dr. Rosy Roberts, she designed translational projects bridging brain imaging and postmortem studies in schizophrenia to characterize glutamatergic neurons at the electron microscopic level. These studies strongly support the relevance of targeting the glutamatergic system for new drug development in this severe mental illness.

Dr. Eliot Lefkowitz is involved in a number of collaborations to investigate the genetic and molecular basis of disease. He provides computational science (bioinformatics) analytical expertise to assist UAB investigators in the processing and understanding of the data they generate in their labs. Our work includes the analysis of genomic sequence data from individuals with Parkinson's disease to better understand how physiological and immune-related pathways are altered in these patients. We also collaborate on research involved in determining the role of the microbiota – the microorganisms that inhabit all parts of our bodies – in health and disease. These studies include looking at the role of microbes in a wide variety of diseases and conditions including cancer, depression, Parkinson's, Alzheimer's, autoimmunity, and many others.

Dr. Frances Lund's laboratory is working on a novel, nasal spray vaccine against SARS-COV2, the virus that causes COVID-19 disease. Although the current injected vaccines efficiently prevent the vaccine recipient from getting an infection in their lungs and feeling ill, the vaccine may not prevent the recipient from getting an asymptomatic infection in their nose and then spreading the virus to others. An nasal spray vaccine, however, would protect the nose and the lung from infection and likely help prevent person-to-person spread of the virus. Such intranasal vaccines could be given painlessly to school-age children, allowing them to return to school with significantly decreased likelihood of transmitting the disease to their family members.

Dr.Ismail Mohamed is applying advanced computational algorithms on magnetoencephalography data for localization of sources of epileptiform discharges, to study sequential brain activation during cognitive tasks at millisecond resolution as well as to study the dynamic interaction between epilepsy and cognitive function. This research aims to minimize the risks and increase success of epilepsy surgery

Dr. Sylvie Mrug studies the impact of individual and environmental factors on mental and physical health in adolescence and adulthood. Current projects focus on the role of early life stress in DNA methylation and cardiometabolic health in adulthood, as well as the role of diet in mental health of adolescents.

Dr. Minae Niwa is dissecting the biological mechanisms by which early psychosocial stress alters adult behavioral patterns related to mood, social cognition, information processing, motivation, and maternal care. Dr. Niwa's preclinical and clinical findings showed a novel link between adverse early life events, sustained neuro-endocrine dysregulation, and long-lasting behavioral deficits. This provides biological insights into psychosocial stress-related behavioral changes and help to find novel interventions and treatments for psychiatric patients with adverse early life events.

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Dr. Vlad Parpura is testing a drug and nanoparticles, both reducing glioblastoma growth in animal models. If translatable to humans, it would aid treatment of this devastating disease.

Dr. Alan Percy leveraged the NIH Rare Disease Clinical Research Network funding to engage clinician-researchers at 14 academic centers across the country, thereby increasing the reach of investigators enrolling participants with Rett syndrome and related disorders including MECP2 Duplication Disorder, males with MECP2 mutations, CDKL5 Deficiency Disorder, and FOXG1 Disorder. These efforts have enrolled more than 1000 individuals with these disorders over the past five years, reducing the knowledge gap greatly, developing clinical trial readiness that has already been applied to these rare disorders, and preparing for the continuation of these activities with funding from the Rettsyndrome.org patient advocacy organization.

Published research by **Dr. Craig Powell**, Director of Civitan International Research Center at UAB, has demonstrated the concept that drugs effective against Alzheimer's Disease may also be effective in

treating patients with Down Syndrome. People affected by Down Syndrome have an extra copy of chromosome 21. Chromosome 21 contains the gene coding for the Amyloid Precursor Protein (APP). Making too much APP leads to too much of the toxic amyloid beta peptide in the brain. This leads to early onset Alzheimer's Disease in people with Down Syndrome. Dr. Powell's research demonstrated that drugs that alter processing of APP, so-called gamma-secretase inhibitors, can prevent production of the toxic amyloid beta peptide and reverse cognitive deficits in a mouse model of Down Syndrome. It remains unclear whether the drug prevents progression to Alzheimer's Disease in the mouse model, or if it works to reduce the intellectual disability in the early years of Down Syndrome. If the first explanation is true, such treatment could prevent worsening of brain function in adults with Down Syndrome. If the second explanation is true, such treatment could actually improve brain function in kids challenged by Down Syndrome; even a small improvement in early Down Syndrome brain function could mean the difference between being gainfully employed versus being relegated to the sidelines for these children. The research demonstrates the concept that any new drug that works in Alzheimer's Disease should also be tested for efficacy in Down Syndrome. Researchers, governments, and pharmaceutical companies around the globe are working around the clock to identify treatments for Alzheimer's Disease and for Down Syndrome.

Dr. Lucas Pozzo-Miller is collaborating with Dr. David Bedwell in the Civitan International Research Center to test the utility of drugs that "skip over" a mutation in the Rett Syndrome gene that leads to premature truncation of the gene's protein product. Such a therapy would allow brain cells to skip reading the mutated portion of the gene that leads to disease, allowing the brain cells to only read the "good parts" of the gene's instructions. This may lead to a revolutionary way to treat Rett Syndrome patients with these truncating mutations. Rett Syndrome is a neurodevelopmental disorder related to both intellectual disability and autism. Dr. Pozzo-Miller's laboratory has been a pioneer in examining brain function in animal models of Rett Syndrome. Dr. David Bedwell's groundbreaking research identifying drugs that can "skip over" genetic mutations has the potential to treat hundreds of neurodevelopmental disorders such as muscular dystrophy, autism, Rett Syndrome, and more. One major goal of the Civitan International Research Center at UAB is to promote collaborative science across laboratories and departments to innovate novel therapies for autism, intellectual disability, and other neurodevelopmental disorders.

With evidence suggesting that elevated blood pressure readings in childhood track to adulthood and that elevations in blood pressure are noted in preschool children, the research of **Dr. Marti Rice** focuses on factors that influence blood pressure in preschool children. It has been noted that weight may not be as big of an influence on blood pressure in preschool children as with adults and that stress and inflammation may be associated with elevations in blood pressure in preschool children.

Dr. Rosalinda Roberts focuses her research on ultrastructural changes in the brain in schizophrenia. Using postmortem human brains she looks at the fine details of the synapse and mitochondria in various brain regions. She has shown different pathological changes related to symptomology and treatment response in schizophrenia. She started and directs the Alabama Brain Collection, which provides brain tissue from neurological, psychiatric and control brains to scientists within and outside of UAB. She is very active in mentoring learners in her laboratory from high school students to junior faculty.

A novel gene therapy for dementia is now advancing to clinical trials in human patients with progranulin mutations. **Dr. Erik Roberson**'s laboratory has demonstrated that gene therapy may provide a novel approach for treating some people with frontotemporal dementia (FTD). His team found that gene

therapy using a vector to restore progranulin expression in brain cells could prevent or reverse dysfunction in animal models of progranulin FTD.

Dr. David Schwebel is among the world's experts in using behavioral strategies to prevent the leading cause of child death in the US, accidental injuries. An abbreviated list of his innovations include using virtual reality to teach children to cross streets, using interactive virtual presence for experts to help parents install car seats properly from a remote location, conducting research to identify how pre-literature toddlers determine safety vs. risk of household products (work that led to international industry change in packaging), and developing interactive websites and podcasts to improve safety in domains ranging from firearms safety to dog bite prevention.

Studies performed in **Dr. Jon Sharer**'s lab helped demonstrate that the litchi fruit is the cause of a mysterious, often fatal illness affecting children in the Muzaffarpur region of India. The onset of acute seasonal encephalopathy has plagued the region for decades, causing hundreds of fatalities, but a collaborative effort between American and Indian scientists solved the riddle. Dr. Sharer's lab showed that samples from patients had clear signs of severe metabolic disturbances caused by toxic substances found in the fruit, which is harvested in the region.

Dr. Robert Sorge was one of the first to highlight the sex differences in the immune cells underlying chronic pain in animal models. Following this work, his lab has explored the ways that diets affect the immune system and contribute to and alleviate pain. To translate this work, his lab completed a pilot clinical trial of diets for knee pain and is working on examining racial differences in diet benefits for knee pain. Finally, he has recently started a novel endeavor to examine how brain circuits involved in fear and learning are altered in chronic pain.

Dr. Christianne Strang's research is focused on retinal functioning in health and disease. She is involved in a collaboration using the retina as a model to elucidate the mechanisms involved in the effects of transcranial current stimulation and a collaboration between the University of Pennsylvania and UAB funded by the National Eye Institute to create detailed characterization of gene expression in human retinal cells and advance our understanding of gene expression and cell type diversity in healthy eyes and in disease states such as Alzheimer's Disease and Age-related Macular Degeneration.

Dr. Jerzy Szaflarski has been investigating the longitudinal effects of acute or chronic injury on human brain plasticity using various imaging methods. Our most recent studies include longitudinal investigations of brain plasticity in response to cognitive behavioral therapy in patients with epileptic and functional seizures, longitudinal effects of pharmacological intervention with cannabidiol in patients with treatment-resistant epilepsy, and of the neuroplastic effects of neurostimulation and neuromodulation. We recently implemented new imaging techniques including MRI-thermometry to measure local brain temperature changes related to neuroinflammation and MREG to measure the effects of seizures and seizure treatments on the glymphatic system.

Dr. Elizabeth Sztul is exploring how mutations in the protein called BIG2 cause microcephaly and inhibit normal brain development. Our studies suggest that BIG2 regulates the transport of essential signaling molecules in neurons and that lack of BIG2 causes the inhibition of neuronal migration required for normal brain development. We are identifying the signaling pathways affected by BIG2 mutations, as means to identify putative targets for therapeutic intervention.

Drs. Edward Taub and **Gitendra Uswatte** have in the past developed a rehabilitation therapy for impaired movement in children with cerebral palsy that is efficacious throughout the entire age range of childhood. It is termed Pediatric CI Therapy and it is now the basis for treatment in a very active clinic at Childrens of Alabama. This therapy was derived from a version of the therapy used with adults. Drs. Taub and Uswatte have recently modified their movement therapy to apply to cognitive impairment in adults after stroke, COVID-19 and associated with aging. Pilot work suggests that the CI Therapy approach works as well in the cognitive domain as it does in the motor area. They have plans to modify the technique so that it can be used with cognitive impairment in children with Down's Syndrome and other conditions.

Dr. Summer Thyme is generating zebrafish mutants to study the function of genes linked to autism and childhood-onset schizophrenia. The behavior, brain development, and brain activity of these mutants will be characterized. The high-throughput zebrafish model will enable screening for drugs that influence brain development, perhaps correcting abnormalities observed in these mutants.

Dr. Tim Townes' lab at UAB is working on a novel way to cure children with sickle cell anemia using the latest CRISPR gene editing technologies that they have modified to achieve even greater specificity than ever before. Sickle cell anemia can lead to early childhood strokes and permanent deficits often called "cerebral palsy". Imagine a world where sickle cell anemia can be cured by taking a child's own bone marrow cells, editing their gene back to typical, and then putting these cells back to make normal red blood cells for the rest of a child's life.

Dr. Janet Turan and her team members are studying how stigma and discrimination affect mental health, healthcare utilization, and physical health outcomes. They are studying health-related stigmas (such as HIV stigma, cancer stigma, and TB stigma) as well as intersectional stigma related to different identities related to race, gender, and economic situation. The team has elucidated important pathways for the effects of stigma on health behaviors, such as medication adherence and attending healthcare visits. In upcoming work, the team will study the effects of stigma in neurocognitive functioning in people living with HIV. Dr. Turan and her team also develop and test interventions to address stigma and increase utilization of HIV prevention and treatment.

Dr. David Vance is studying the cognitive training protocols to protect and improve cognitive functioning in people as they age, focusing specifically in adults with HIV and cancer who may have brain fog and be at risk for cognitive decline. Much of his recent work shows that not all cognitive training programs are the same. Certain combinations of training (e.g., speed of processing training, executive functioning training) may be more effective in improving overall cognitive functioning compared to others. Such cognitive training can also help people improve their driving safety and promote better quality of life.

Dr. Deborah Voltz's most recent research focuses on the role teacher education plays in enhancing the retention rates of beginning teachers in high-poverty urban schools, as teacher experience has been found to be a critical variable in student achievement. This research examined the career paths of the graduates of UAB's Urban Teacher Enhancement Program who began teaching in urban schools. Their longevity in urban teaching was examined at the first-, fifth-, and tenth-year mark and compared to national averages. Participants also were interviewed to determine their greatest rewards and challenges in urban teaching, their perspectives regarding their reasons for entering and/or staying in urban teaching, and their thoughts about the role their teacher education program played in their career trajectory. Findings indicated that retention rates of study participants compare favorably with national averages, and that

program participants felt that their teacher education program had a positive influence on their longevity in urban teaching, with specific program features being noted as particularly helpful.

Dr. Jianhua Zhang's laboratory is using novel mouse models to test the hypothesis that enhancing autophagy, lysosomal activities help mitigate metabolic and proteotoxic stress. Success of these studies will provide significant insights into pathogenesis and therapeutic targets of cognitive, neurodevelopmental and neurological diseases.