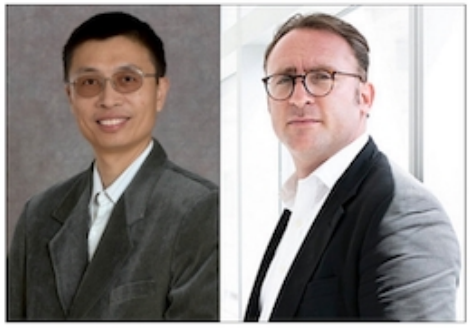
The Virtual Center for VCFS: www.vcfscenter.org

Newsletter #5 | Current News | December, 2020

News from the Lab at Columbia University and the New York State Psychiatric Institute

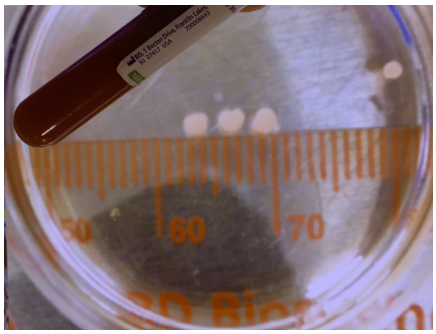
Psychiatric Research Edition

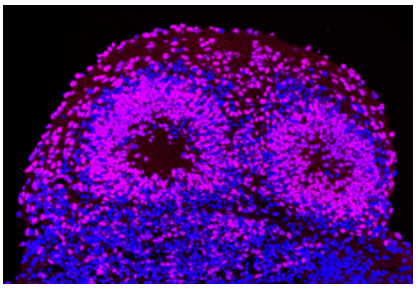
As we have reported to those of you who are registered with The Virtual Center for Velo-Cardio-Facial Syndrome, several years ago we began a collaboration with the Department of Psychiatry at Columbia University Medical Center in New York City. The purpose of the collaboration was to focus on the treatment of mental disorders in people with VCFS. Although there have been hundreds of research projects and publications focusing on VCFS, very few have discussed treatment, and most of the reports that discuss treatment are limited to case reports of single individuals or a small series of cases. Most of those reports are retrospective, meaning that they report the results of this medication or that medication after the treatment has been applied. A variety of conclusions have been drawn, but in reviewing our experience with many hundreds of people with VCFS who have not had positive outcomes with treatment of disorders ranging from generalized anxiety to severe treatment-resistant psychosis, it is clear that there is no single magic bullet. Therefore, the approach taken by our team of Dr. Gianni Faedda, our psychiatry expert, and our valued colleagues at Columbia, Drs. Sander Markx, Joseph Gogos, Bin Xu, Martin Lackinger and Pratibha Thakur has been to personalize the process of analyzing brain formation and function in individuals. In other words, we believe that in the world of mental and cognitive disorders, VCFS is not only a special case, but likely a unique case of brain development and function. Unique cases deserve unique solutions, and our way of thinking is that individualized treatments are not only possible, but the answer for which we have all been searching. Dr. Markx is Director of the Precision Psychiatry program at Columbia and his interest in VCFS is a natural fit for this approach. In this issue of our Newsletter, we introduce you to this superb research team and their work. The following reports are from Bin Xu, Ph.D., Sander Markx, M.D., Pratibha Thakur, Martin Lacking, Ph.D., and Joseph Gogos, M.D., Ph.D. The paragraph below from Dr. Xu describes some of his current work that involves VCFS and has been advancing with the assistance of The Virtual Center for VCFS and its registrants who have volunteered to be subjects in research studies being performed in the labs at Columbia. More than 100 people have been subjects in the study; 50 with VCFS-related psychosis and rest being their first degree relatives. They have participated in both federally funded and privately funded research that will provide information about the direct cause of psychosis in VCFS, and also treatments that would be most effective for that specific individual. The project has involved the development of iPSCs (induced Pluripotent Stem Cells). These cells are gathered from a blood draw from the arm and reprogrammed to become neurons that are identical to the neurons in the brain of the person who is being studied. These neurons are then developed into brain organoids, often referred to as “minibrains” (see the photos in this article) that can be studied and exposed to various chemicals and medications that might improve their structure and function.

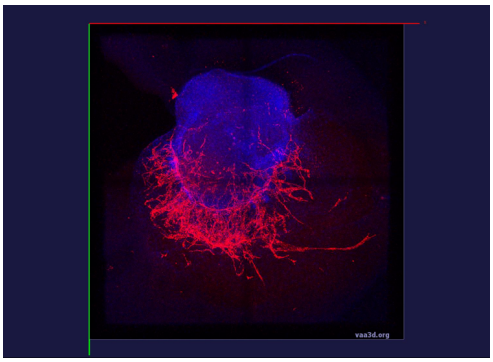


The following two paragraphs are from Dr. Bin Xu and Dr. Sander Markx at Columbia University and the New York State Psychiatric Institute, and Pratibha Thakur, Martin Lacking, Ph.D. and Joseph Gogos, M.D., Ph.D. of the Zuckerman Mind, Brain and Behavior Institute of Columbia University. The first section is from Dr. Xu and Dr. Markx and the second from Drs. Thakur, Lacking, and Gogos. In our next edition, we will hear about clinical management from Dr. Faedda.

Our lab is developing a brain organoid model to investigate cellular and molecular mechanisms underlying human neurodevelopmental disorders. We have chosen the well-defined genetic disorder, velo-cardio-facial syndrome (also known as DiGeorge syndrome or 22q11.2 DS) to determine the cellular and molecular mechanisms associated with high risk for psychosis. Using advanced technology, we conducted a comprehensive transcriptome analysis from 70-day old cerebral organoids from VCFS cases and their first degree relative controls who do not have VCFS. Transcriptome refers to the entire RNA transcription of the DNA in the cells. Transcription is how information from the DNA in a cell's nucleus is transported to the ribosomes in the cell and eventually developed into proteins that determine genetic traits, including both physical and behavioral information. Several cell types present in fetal brain tissue are detected in our organoids. Our analysis of different cell types in the organoids shows that control subjects have a higher proportion of differentiated excitatory neurons compared to VCFS organoids. Analysis of gene expression in control organoids compared to VCFS neurons shows better regulation of genes related to neuron differentiation, maturation and growth relative to control neurons. We have also shown that neurite (axon and dendrite) complexity in neurons from VCFS organoids is reduced compared to the control organoids. These findings combined with other RNA data from neurons indicate a defect in neuron differentiation and growth in VCFS organoids compared to controls. Our research work is providing critical insights for development of new therapies for mental illness and cognitive dysfunction in VCFS. ***Bin Xu, Ph.D.and Sander Markx, M.D.***







Above left: organoids developed from a blood sample; center: gene expression in an organoid cut to show ventricle formation; right: an organoid with developing vascular supply.

Thank you, Drs. Xu and Markx. To recap the importance of this investigation, the actual properties of brain function in people with VCFS and how the cells in their brains function can now be determined. These experiments are done on exact copies of brain tissue from the research subjects but it is done without risk to the people who are participating. Very soon, we will determine how medicines effect their brains, and find out which medicines would work to correct malfunctions of the brain in each individual patient. We have learned that one size does not fit all and reaction to medication is individual. We are entering the age of specificity, not for the diagnosis of VCFS, but for a specific individual's neural response.

Finding new therapies for psychosis in VCFS

Pratibha Thakur and Dr. Martin Lackinger, neuroscientists at Columbia University in New York, are aiming to decipher the molecular mechanisms of psychotic symptoms related to the 22q11.2 deletion that causes VCFS in an effort to accelerate novel therapies. In their recent study, supervised by the Zuckerman Institute's principal investigator and schizophrenia expert, Dr. Joseph Gogos and their collaborators at the Psychiatry Department of Columbia University Medical Center, Dr. Bin Xu and Dr. Sander Markx, these scientists examined the role of a potential therapeutic component aiming to repress a gene that was previously found to be significantly upregulated in a mouse model of VCFS. Upregulation occurs when cellular receptors are created, or more strongly expressed from instructions in the DNA of the cell. Using neuronal cell cultures generated out of stem cells from blood samples of individuals with VCFS who are psychotic, the researchers were able to demonstrate that the previously identified gene is also upregulated in human neurons. Furthermore, by repressing this specific gene in the adult mouse brain, the researchers were able to normalize social memory impairments in these animals. Social memory affects how people process and apply information about other people and social situations, a set of processes commonly affected in VCFS. These exciting findings support the conclusion that the molecular mechanism behind this gene dysregulation could help us develop therapeutics to treat specific VCFS-related psychotic illness. ***Pratibha Shakur, Martin Lackinger, Ph.D., Joseph Gogos, M.D., Ph.D.***

Pratibha Thakur (left), performed the mouse drug treatments and investigated behavioral assays. Dr. Martin Lackinger (middle) performed the human neuronal culture experiments. Dr. Joseph Gogos (right), principal investigator and supervisor of the recent 22q11DS study. For more information, please visit https://gogoslab.zuckermaninstitute.columbia.edu/ Questions may be directed to Dr. Shprintzen at robert.shprintzen@vcfscenter.org or via the contact page on our web site at www.vcfscenter.org.