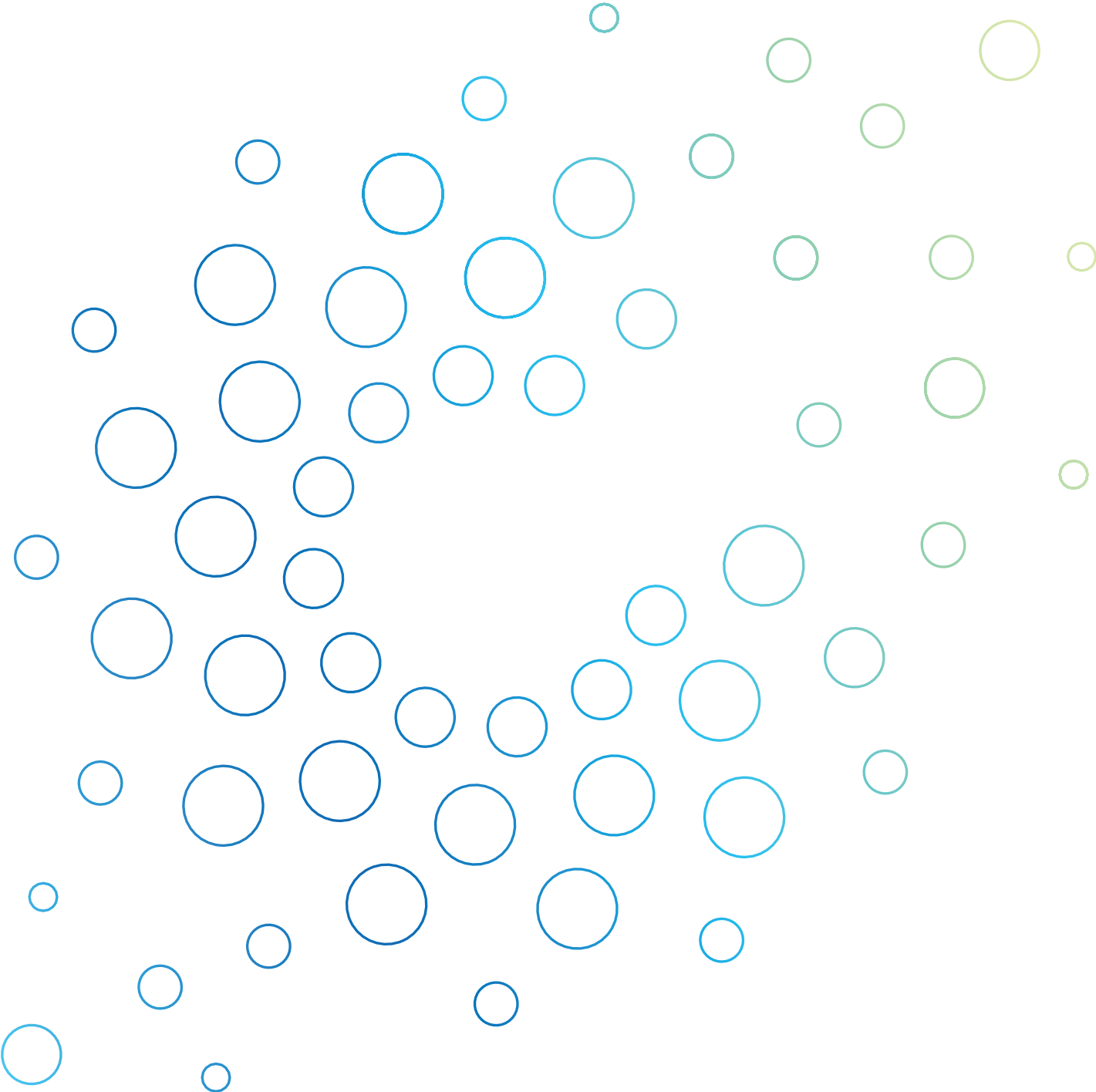POITRAS CENTER FOR
PSYCHIATRIC DISORDERS RESEARCH

IMPACT REPORT

2021–2023

The goal of the Poitras Center for Psychiatric Disorders Research is to advance human health through brain research by addressing mental disorders that have a devastating impact on patients, their families, and society at large.
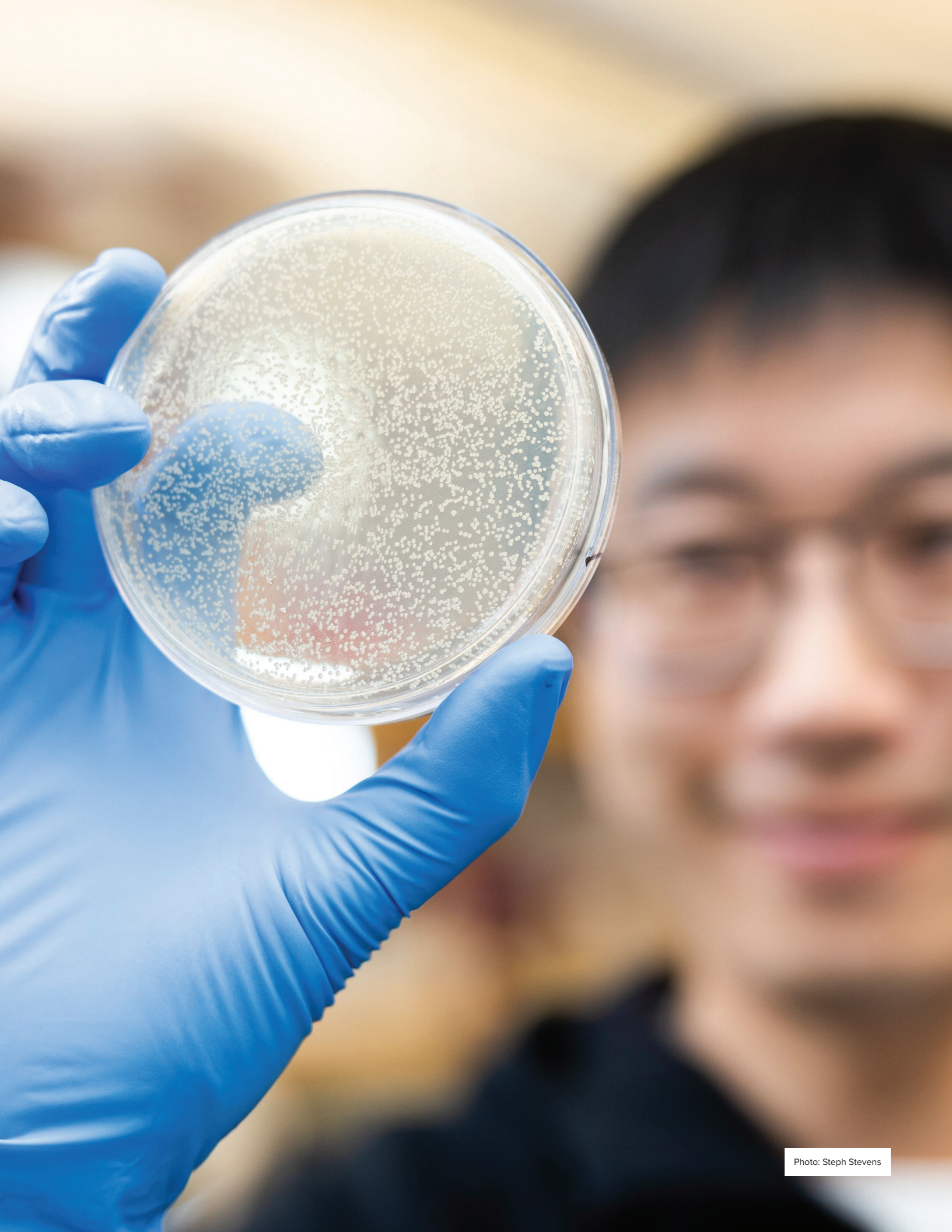
Letter from the Director

It has been 16 years since the founding of the Poitras Center for Psychiatric Disorders Research, and our scientists continue to break new ground in uncovering the mechanisms driving major mental illness. Over the past two years, discoveries in the labs of Poitras investigators have ranged from harnessing the power of artificial intelligence to predict risk for bipolar disorder before its onset to identifying common targets for therapeutics to treat different neuropsychiatric diseases that share common symptoms.

These exceptional advances, made possible by the generous support of the Poitras family, have the potential to help increasing numbers of people earlier in their lives — and to even interrupt the path from health to disease.

A SMALL SAMPLING OF OUR PROGRESS

Feng Zhang's team has developed a computational pipeline to identify dozens of RNA-guided systems in nature that could become promising methods to target mutations driving neuropsychiatric diseases. Among them are the OMEGAs, ancient DNA-cutting enzymes whose small size gives them an advantage over current CRISPR gene-editing systems in delivering cargo to cells.

Inserting large stretches of DNA safely and efficiently in the genome is a major challenge in the gene-editing field. The Zhang researchers have now moved forward to meet it: They have delineated the structure and are characterizing the molecular mechanisms of a genetic element called R2 that can be engineered to precisely target and insert an entire replacement gene in human cells.

Guoping Feng's lab is at the forefront of generating animal models of neuropsychiatric and neurological disorders. The team launched the first-ever nonhuman primate study of a gene-therapy treatment for a neurological disorder; early results demonstrate successful reversal of cognitive and behavioral symptoms. Using a mouse model, they found that the absence of a protein required for transfer of information between neurons results in symptoms common in both bipolar disorder and schizophrenia, including hyperactivity and impulsivity. Understanding the mechanisms underlying such symptoms in animal models sets the stage for developing targeted therapies for those symptoms in humans.

The labs of John Gabrieli and Susan Whitfield-Gabrieli continue to excel at predicting risk for psychiatric disorders in children and adolescents. With colleagues at Massachusetts General Hospital, Gabrieli's lab pioneered the first machine-learning model to predict bipolar disorder in youth — an important step toward developing a simple risk calculator for clinicians. One neuroimaging study co-led by them revealed reduced volume and activation in a brain region associated with reward in adolescents diagnosed with anxiety and/or depression; another found that children at risk for psychosis show slower brain activity during a working memory task. Such biomarkers hold the promise of enabling interventions that could prevent or reverse progression of psychiatric disorders.

As these pages show, the support of the Poitras family continues to be transformative. We are, as always, deeply grateful to them. Their generosity brings hope to the individuals and families touched by major mental illness.

Robert Desimone, PhD

Doris and Don Berkey Professor in Brain and Cognitive Sciences
Director, McGovern Institute for Brain Research, MIT

RESEARCH

The latest advances in the Poitras Center include harnessing the power of AI to predict risk factors for psychiatric disorders, targeting cerebellum networks for precision therapeutics, finding diagnostic biomarkers for impairments in schizophrenia, using a CRISPR activation screen to identify genes underlying disease, discovering a new class of DNA-cutting enzymes, and advancing a breakthrough in correcting genetic mutations.

Human Studies

Poitras Center investigators John Gabrieli and Susan Whitfield-Gabrieli combine powerful images of human brain activity and structure with behavioral testing to reveal the basis of psychiatric disorders.

In collaboration with clinicians and researchers around the world, they have helped revolutionize the role of neuroimaging alone and in concert with new technologies, including artificial intelligence (AI). Among other recent advances, they've discovered neural mechanisms that predict risk for psychiatric disorders in children, found evidence for the efficacy of mindfulness-based neurofeedback for affective disorder, and identified brain regions to target for the treatment of major depression.

Gabrieli, the Grover Hermann Professor of Health Sciences and Technology and Cognitive Neuroscience, is director of the Athinoula A. Martinos Imaging Center at MIT. Whitfield-Gabrieli is director of the Northeastern University Biomedical Imaging Center. Here are some of the research highlights from their labs.

Predicting risk for psychiatric disorders

HARNESSING THE POWER OF AI

With colleagues at Massachusetts General Hospital, Gabrieli's lab has pioneered the first quantitative machine-learning model to predict bipolar disorder in youth. Machine learning is a subfield of AI that finds patterns in large, complex data sets.

Though bipolar disorder often begins in adolescence, the condition may be overlooked or misdiagnosed until patients are older. "Early detection of risk for the disorder would enable clinicians to provide more proactive support and treatment as well as a road map for the future for patients and their families," says Gabrieli. For their study, the researchers obtained data from 492

participants in a 1990s Mass General study on attention deficit–hyperactivity disorder. These data contained extensive psychiatric assessments of children and teenagers at baseline and over 10 years of follow-up. By applying a machine-learning algorithm, the team successfully identified 75 percent of the 45 individuals who later developed bipolar disorder. The predictors best at revealing those who developed bipolar disorder — combined problems with attention, aggression, and anxiety — came from the Child Behavioral Checklist assessment tool. The researchers' machine-learning approach performed better than any other method of predicting bipolar disorder to date. "With further refinement, this tool could be used to develop a simple risk calculator for health care providers," says Gabrieli.

To learn whether language features associated with psychosis risk are universal, Whitfield-Gabrieli collaborated with Shanghai Mental Health Center researchers, among others, in a study of 46 Mandarin-speaking youths at the center (20 at clinical high risk, 25 healthy controls). In their assessment, the team used both acoustic analysis and natural language processing, which has been shown to reveal decreased coherence and content complexity in schizophrenia and in those at clinical high risk for psychosis. Natural language processing combines machine learning with computational linguistics to enable computational analysis of large, complex sets of words and phrases.

For the study, they entered the contents of interviews with participants — both the original Mandarin and an English translation — into natural language processing systems specific for each language. Using the variables of coherence, complexity, and emotional valence, they found that both natural language processing systems

John Gabrieli's lab has pioneered the first quantitative machine-learning model to predict bipolar disorder in youth. Photo: Steph Stevens

accurately identified those at high risk for psychosis based on linguistic or acoustic features. Breaking new ground, they found that the Mandarin-specific system identified an increased use of "localizers" — words that express the relative position of objects (say, "on" versus "in") — among participants at higher risk. The study highlighted the importance of using both English-specific and language-specific natural language processing approaches while assessing psychiatric risk in people from around the world.

OPENING A WINDOW INTO THE MIND

Gabrieli and Whitfield-Gabrieli — with researchers from institutions including the Netherland's Utrecht Brain Center and Boston's Massachusetts Mental Health Center — used functional magnetic resonance imaging (fMRI) to explore whether children ages 7-12 with a parent or sibling diagnosed with psychotic illness showed altered brain activity during a working memory

> " Our aim was to develop new ways to classify mental illness based on underlying neural markers that cut across diagnostic boundaries, enabling development of more holistic therapies. "
>
> –JOHN GABRIELI

HUMAN STUDIES

task compared to healthy controls (17 children with relatives with psychotic illness, 20 controls). fMRI measures changes in blood oxygenation across the brain to locate where neural activity is taking place.

The researchers scanned the children's brains while they viewed a sequence of stimuli, one by one, and had to decide if the current stimulus was the same as one presented in an earlier trial. Children with diagnosed family members showed significantly lower working memory scores and slowed activation in brain regions critical to recollection and episodic memory retrieval. "Schizophrenia is known for exceptional symptoms, like auditory hallucinations or paranoid delusions, but difficulties in working and long-term memory are core symptoms associated with problems in social function and academic performance," says Gabrieli. "These findings suggest that these memory problems in childhood may increase the likelihood of full expression of schizophrenia, which typically occurs in later adolescence or early adulthood."

While fMRI shows activity in brain regions based on blood flow, magnetic resonance imaging (MRI) shows detailed structural images of the organs and tissues in the body, including anomalies. Gabrieli, in collaboration with researchers at Massachusetts General Hospital and Harvard Medical School, added diffusion weighted imaging to MRI to focus on the brain's "white matter," the insulated fibers that connect the billions of neurons in the human brain to facilitate the transfer of information. Diffusion weighted imaging is a method to evaluate the micro-architecture of tissues in the human body. When the team conducted brain scans of 32 children ages 6-12, they found that reduced white-matter connectivity in a pathway linked to emotional dysregulation correlated with elevated scores on the Child Behavior Checklist Anxiety/Depression scale — a known predictor of major depression. The findings could help clinicians develop a biomarker that identifies major depression in children earlier and more effectively than behavior and self-reports.
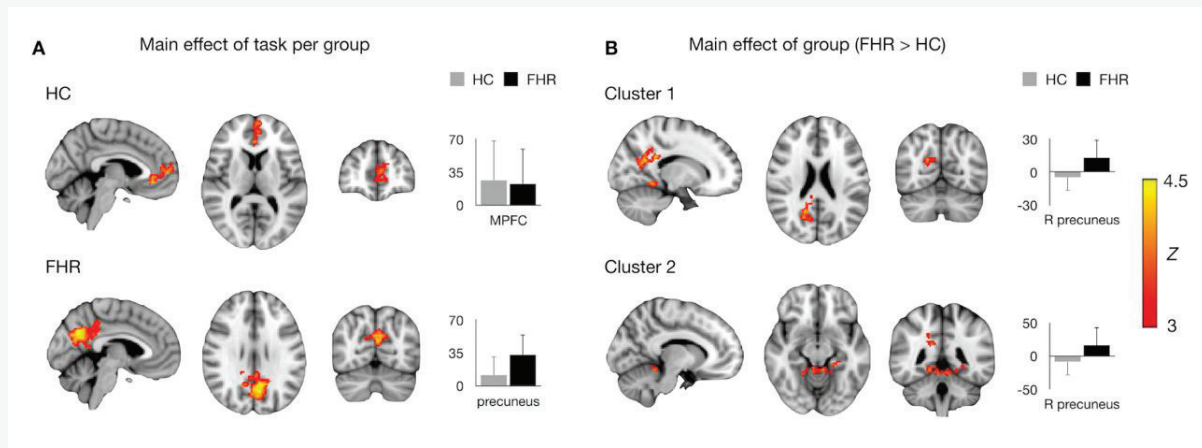
Children with family members diagnosed with psychotic illness (FHR) showed significantly lower working memory scores and slowed activation in brain regions critical to recollection and episodic memory retrieval compared with healthy controls (HC). Image courtesy of the researchers

While in the scanner, participants practiced mindfulness meditation using a paradigm they had learned to help reduce activation in the default mode network — a network that is most active when a person is not focused on any particular task — to alleviate depression and anxiety.

MRI scanner

Real-time fMRI data transfer

Feedback projection

fMRI neurofeedback

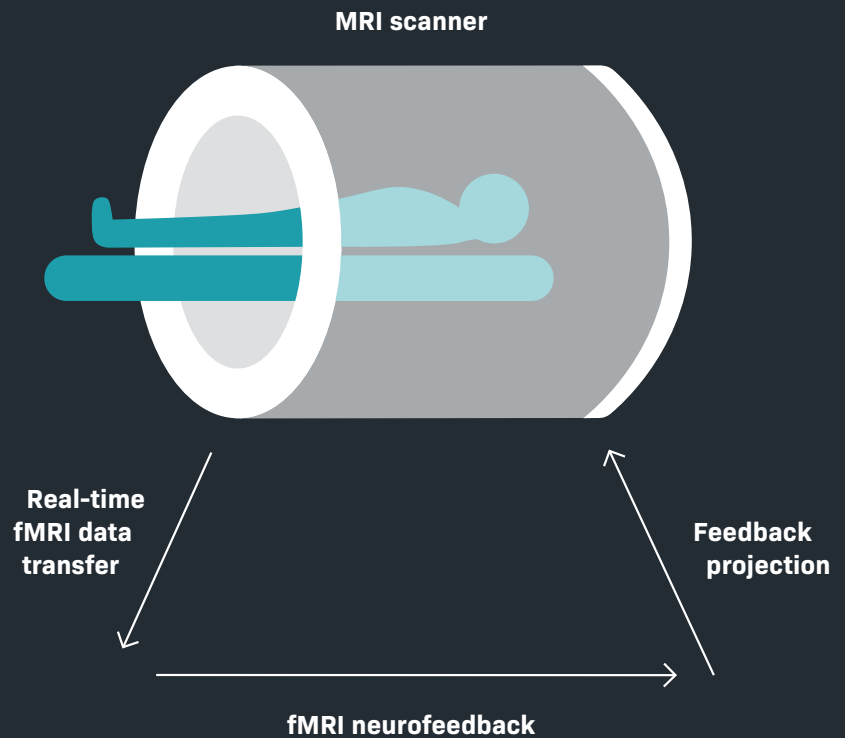Image: OPUS

New interventions for adolescents

GOING BEYOND TRADITIONAL DIAGNOSTIC BOUNDARIES

According to the NIH's 2022 National Healthcare Quality and Disparities Report, nearly 20 percent of U.S. children and teens have a mental, emotional, developmental, or behavioral disorder, and suicidal behaviors among high school students increased 40 percent from 2009 to 2019.

The Boston Adolescent Neuroimaging of Depression and Anxiety study, co-led by Gabrieli and Whitfield-Gabrieli as part of the Human Connectome Project, has revealed important insights into the brains of youth ages 14-17 diagnosed with anxiety and/or depression. "Our aim was to develop new ways to classify mental illness based on underlying neural markers that cut across diagnostic boundaries, enabling development of more holistic therapies," says Gabrieli.

Over six months, the team of 15 researchers, who were affiliated with 11 different institutions, scanned the brains of 129 adolescents with a depressive and/ or anxiety disorder as well as 64 adolescents with no psychiatric history as they performed a task where they could win or lose actual money. The depressed-anxious participants showed reduced volume and activation in the nucleus accumbens — a key region associated with reward — upon receipt of the money, along with alterations within the structure of the nucleus accumbens. Clarifying how deficits in the nucleus accumbens impact reward-related circuitry could lead to powerful interventions to alleviate symptoms of anxiety and depression early in life.
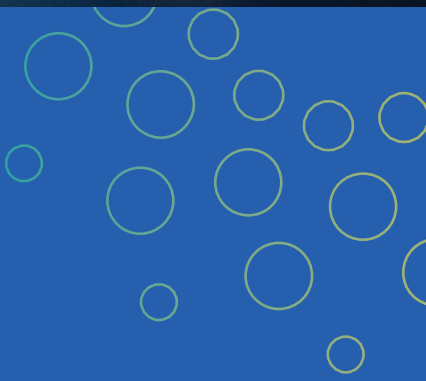
NEUROFEEDBACK TO ALLEVIATE DEPRESSION, ANXIETY

Can real-time feedback about brain activity help adolescents alleviate symptoms of major depressive disorder and anxiety? In a proof-of-concept study, Whitfield-Gabrieli used fMRI to show nine teens ages 17-19 with a history of depression and/or anxiety what was

Susan Whitfield-Gabrieli collaborated with Shanghai Mental Health Center researchers to learn whether language features associated with psychosis risk are universal.
Photo: Adam Glanzman/Northeastern University

happening in their brains as they practiced mindfulness meditation inside a scanner. "Once people know how to do mindfulness meditation, they can do it on their own anytime, anywhere," says Whitfield-Gabrieli. Mindfulness meditation, wherein practitioners focus their awareness on the present moment, can modulate activity within the brain's default mode network, a network that is most active when a person is not focused on any particular task. Two hubs within this network are engaged when we think about the past or the future. In depression, thinking about the past may turn into rumination, and in anxiety, thinking about the future may turn into obsessive worrying. These hubs are often hyperconnected in people with depression or anxiety. While in the scanner, the participants practiced mindfulness using a paradigm they had learned to help reduce default mode network activation. "Network connectivity was reduced with increased mindfulness for each participant," says Whitfield-Gabrieli.

"
Our study highlights the promising role of specific functional and anatomical targets for noninvasive therapies, including transcranial magnetic stimulation.
"

—SUSAN WHITFIELD-GABRIELI

Targeting cerebellum networks for precision therapeutics

USING MORE-ADVANCED TECHNOLOGY TO BENEFIT TREATMENTS

The cerebellum plays a vital role in most physical movement. Located just above and behind where the spinal cord connects to the brain, it's also involved in cognitive and affective processing. Functional connectivity abnormalities in the cerebellum have been reported in individuals with schizophrenia and those at high risk for psychosis. Whitfield-Gabrieli has studied the role of the cerebellum — particularly a deep cluster of neurons within it known as the dentate nuclei — in psychotic disorders. She found that advances in MRI — that is, using a 7T MRI, which provides images of much higher resolution and better tissue contrast, rather than a 3T MRI — provide a greater understanding of the disruptions in dentate nuclei circuitry contributing to psychotic disorders. These findings will enable more refined treatments using deep brain stimulation and other strategies. The 7T MRI provides additional benefits. "Functional changes in brain network organization, combined with behavioral measures, can be used to predict disease onset before symptoms appear," says Whitfield-Gabrieli.

IDENTIFYING TARGETS TO TREAT MAJOR DEPRESSIVE DISORDER

Neuroimaging studies have shown aberrant structure and function of the cerebellum in major depressive disorder. Whitfield-Gabrieli, with colleagues from the University of Toronto and other Canadian and U.S. institutions, conducted an fMRI study (148 participants with major depressive disorder, 99 healthy controls) to explore the role of the circuitry connecting the cerebellum and the neocortex — the largest part of the cerebral cortex — in the disorder. The neocortex is central to higher-order brain functions including sensory perception, cognition, spatial reasoning, and language.

Whitfield-Gabrieli found that 7T MRI, which generates images of much higher resolution and better tissue contrast than 3T MRI, provides a greater understanding of the disruptions in dentate nuclei circuitry contributing to psychotic disorders.

Compared to healthy controls, participants with the disorder displayed increased functional connectivity within the circuity's default mode network. They also showed significantly elevated functional connectivity between three cerebellar regions as well as the angular gyrus, which is involved in semantic and number processing, attention, and social cognition. "These findings highlight the promising role of these functional and anatomical locations for the development of targets for noninvasive therapies, including transcranial magnetic stimulation," says Whitfield-Gabrieli.

Cellular and Systems Research

Plumbing the inner workings of cells and their related circuitry provides insight into what goes right in the healthy brain and what mechanisms can break down in disease. The labs of Poitras Center investigators Guoping Feng and Feng Zhang continue to make breakthroughs in identifying disrupted neural circuits that can serve as targets for novel therapies for neuropsychiatric disorders.

Among other advances in the lab of Feng, the James W. (1963) and Patricia T. Poitras Professor in Brain and Cognitive Sciences, researchers have identified dysfunctional circuits common to more than one major mental illness, accelerating potential development of common therapies to treat more patients.

New research approaches and findings from the lab of Zhang, the James and Patricia Poitras Professor of Neuroscience, include innovative screens to identify genes that can drive cell fate changes as well as modulate cellular responses to drugs. These approaches provide a road map for researchers worldwide to generate tailored models of disease and discover potential drug therapy targets.

Here are some of the recent advances from their labs.

Feng lab: Revealing the mechanisms driving neuropsychiatric disorders to advance therapeutics

TARGETING COMMON CIRCUITS TO TREAT DIFFERENT PSYCHIATRIC DISORDERS

Certain neuropsychiatric disorders share similar symptoms. Cognitive impairment, for example, is a common feature of both autism and schizophrenia. Feng's lab has found in mouse models that a common circuit mechanism in the thalamus drives a specific type of cognitive impairment in some cases of both autism and schizophrenia, even though there are diverse genetic causes for each disorder. The thalamus is a structure near the center of the brain that relays sensory and motor signals to the cerebral cortex for interpretation and also plays a critical role in memory, navigation, attention, and cognition.

To explore the genetic piece of the puzzle, the researchers used the gene-editing tool CRISPR-Cas9 to knock down the expression of two autism risk genes and one schizophrenia risk gene in the mouse models. The knockdown mice exhibited compelling contextual memory deficits, and the neurons themselves fired excessively. The team was able to turn down hyperexcitability and reverse cognitive deficits in the mice with both disorders with a cutting-edge method not yet approved for humans called chemogenetics, which uses chemically engineered receptors and designer molecules specific for those receptors to modulate the activity of cells. The findings show the potential to help increasing numbers of people by addressing common symptoms across different disorders using circuit manipulation, and identifying cells in those circuits as potential drug targets.
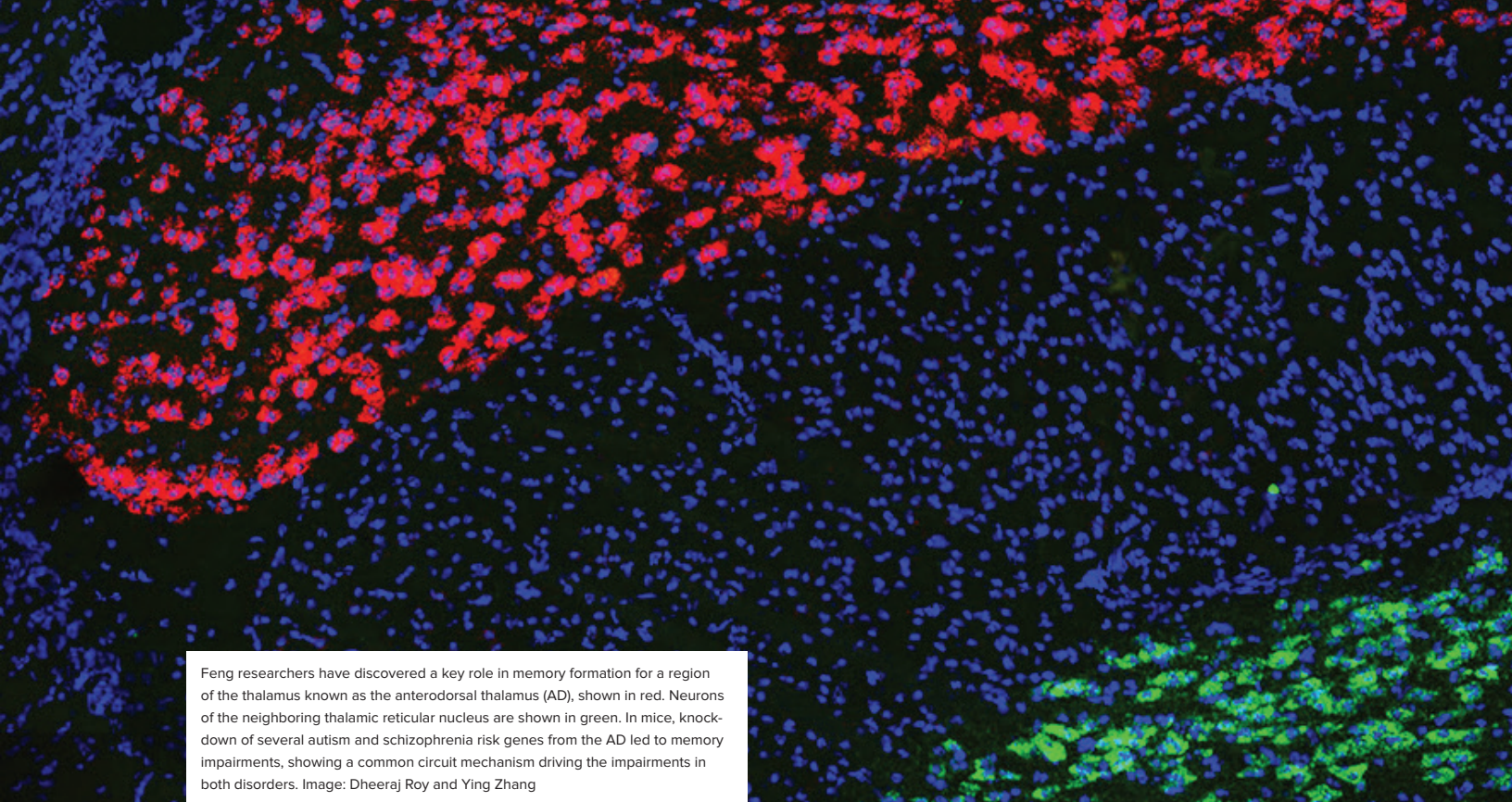
Feng researchers have discovered a key role in memory formation for a region of the thalamus known as the anterodorsal thalamus (AD), shown in red. Neurons of the neighboring thalamic reticular nucleus are shown in green. In mice, knock-down of several autism and schizophrenia risk genes from the AD led to memory impairments, showing a common circuit mechanism driving the impairments in both disorders. Image: Dheeraj Roy and Ying Zhang

"From a therapeutic point of view, you may not want to go after individual genetic mutations because they may be unique to a very small percentage of patients," says Feng. "But at a higher level, at the cellular or circuit level, there may be more commonalities." Those commonalities open the door to the potential for a common therapeutic intervention to address symptoms of various disorders.

UNCOVERING CLUES TO TREAT BIPOLAR DISORDER, SCHIZOPHRENIA

Many risk genes for neuropsychiatric disorders, including bipolar disorder and schizophrenia, encode "postsynaptic proteins," which enable the transfer of information from one neuron to others. They play a critical role in the development, function, and plasticity of synapses—the small connectors between neurons where that information, in the form of electrical signals, is transmitted.

Researchers in Feng's lab, in collaboration with researchers in Shanghai, have found that mice engineered to lack one of those postsynaptic proteins (SAPAP4) have abnormalities in neurons in the prefrontal cortex as well as abnormal amounts of four additional key postsynaptic proteins.
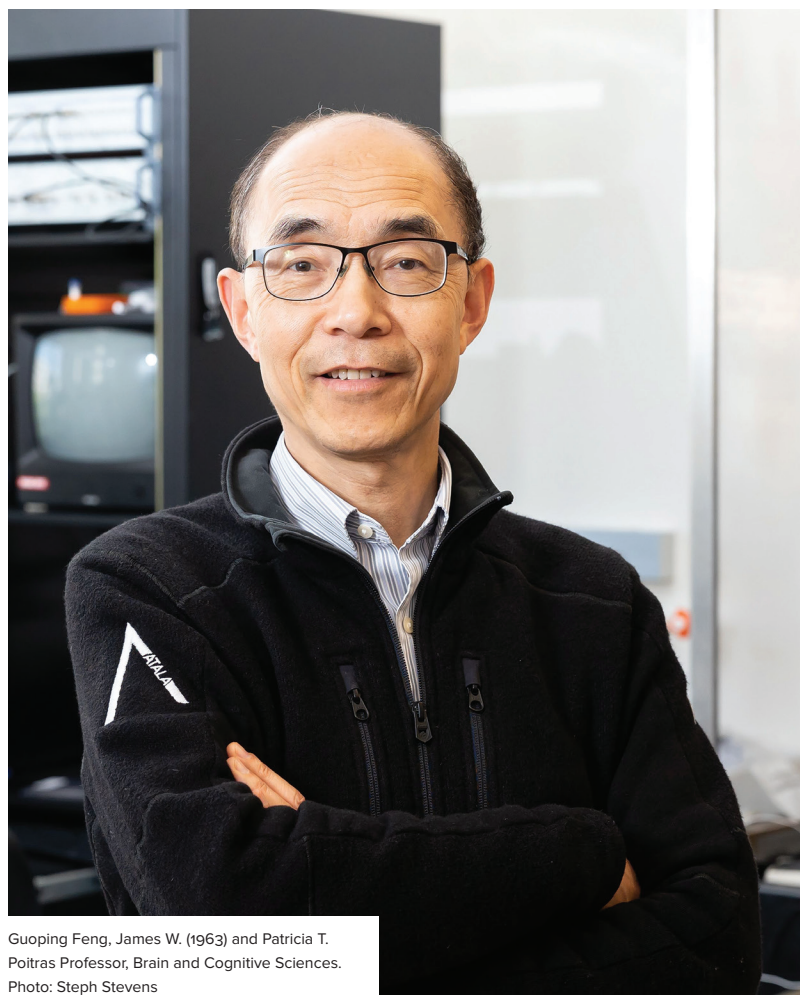
Guoping Feng, James W. (1963) and Patricia T. Poitras Professor, Brain and Cognitive Sciences. Photo: Steph Stevens

The researchers found that those structural and functional abnormalities significantly affected the behavior of the mice, which exhibited symptoms connected with mania. Among them were hyperactivity, impulsivity, reduced depressionlike behavior, and memory deficits. When the team gave the mutant mice valproate, a mood stabilizer used to treat mania, the hyperactivity decreased.

"Together our findings show that SAPAP4 plays an important role in healthy synaptic function," says Feng. "Discovering the mechanisms underlying its absence provides important clues for developing potential therapies for neuropsychiatric disorders characterized by hyperactivity."

FINDING DIAGNOSTIC BIOMARKERS FOR IMPAIRMENTS IN SCHIZOPHRENIA

Disruptions in the thalamocortical circuit, which plays a critical role in sensory processing and cognition, have been implicated in a range of symptoms in schizophrenia, including delusions and disordered working memory. In particular, brain oscillations — the synchronized electrical activity generated spontaneously by neurons in response to stimuli — in the thalamocortical

circuit have been shown to be abnormal in patients with schizophrenia.

To explore what mechanisms might be driving the disruptions, researchers in the Feng lab used electroencephalography (EEG) — which measures the electrical activity of the brain produced by neurons firing simultaneously — on two types of model mice: those missing the *CACNA1g* gene, which encodes a protein that regulates neuron activity, and those with reduced function of the *CACNA1g* gene. They also used EEG on wild-type mice for comparison. They found that two patterns of synchronized electrical activity were disrupted in both types of model mice. "The study recapitulated the EEG deficits often observed in patients with schizophrenia," says Feng.

The researchers are now working to pin down which specific types of neurons are affected that lead to the abnormal brain activity. Research has shown that mutations in 10 different genes strongly increase an individual's risk of developing schizophrenia. The team plans to use the EEG technique in mouse models of schizophrenia with the other nine genes as well.
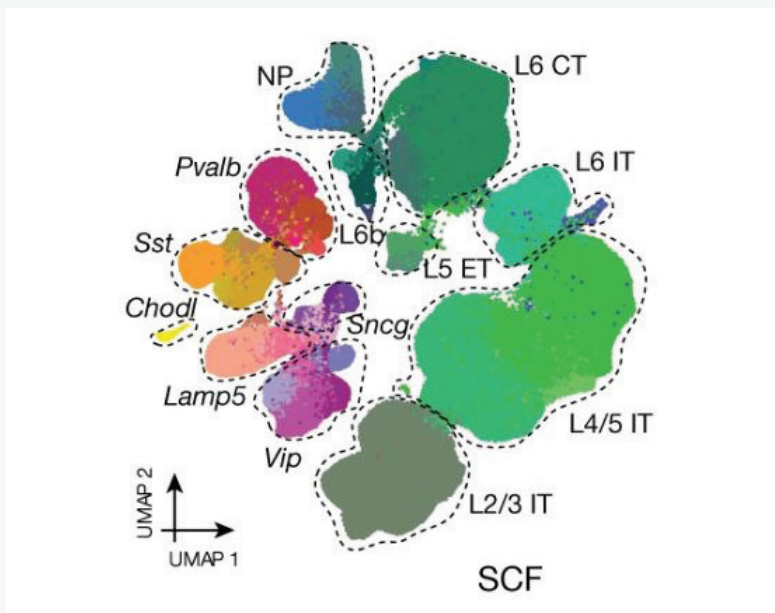
UMAP representation of the mouse transcriptomic–epigenomic integrated molecular taxonomy. UMAP is a technique that constructs a graph representation of the data collected. Image: BRAIN Initiative

This atlas classifying cell types from typical brains opens the door to learning what goes wrong in brain diseases and is an initial step in mapping the entire mammalian brain to reveal which cells and connections drive disorders ranging from Alzheimer's to depression.

"We want to identify shared and distinct changes resulting from the different high-risk genes, not only to facilitate our understanding of the pathophysiology of schizophrenia but also to develop potential diagnostic biomarkers for specific impairments in patients and pave the way for therapeutics to treat them," says Feng.

EXPEDITING THE TRANSITION OF ANIMAL RESEARCH TO THE CLINIC

The NIH's Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, a consortium comprising hundreds of researchers from around the world, has for the first time mapped the millions of neurons and other cells in the primary motor cortex of the human, mouse, and monkey brains—a brain region similar across all mammalian species that controls movement. The lab of Feng, a principal investigator in the initiative, focused on generating and processing single-cell RNA-sequencing and single-nucleus RNA-sequencing data—a method critical for understanding the genes an individual cell switches on, how those genes are regulated, and details including the cell's properties, shape, and location. This atlas classifying cell types from typical brains, including how they compare across the three species, opens the door to learning what goes wrong in brain diseases characterized by movement dysfunction, such as amyotrophic lateral sclerosis (ALS). It is also an initial step in mapping the entire human brain to reveal which cells and connections drive neurologic and neuropsychiatric disorders from Alzheimer's to depression,

enabling researchers to identify precisely which circuits to target in developing new therapies.

The data and tools in the study are publicly available. "This body of work provides a road map for exploring cellular diversity and organization across brain regions, organ systems, and species," write the authors. Says Feng: "We expect this multimodal, multispecies cell census and atlas to accelerate the transition of research in animal models to possible clinical applications in humans."

Zhang lab: Identifying targets for research, novel treatments

ACCELERATING ENGINEERING EFFORTS TO DEVELOP INTERVENTIONS FOR NEUROPSYCHIATRIC DISORDERS

Transcription factors are proteins that control which genes are turned on. The set of genes turned on governs the type of cell that will result, such as a T cell or a liver cell, as well as the state the cell is in, for example, healthy or exhausted. Zhang's lab has created a transcription factor atlas for human cell types. Knowing which transcription factors generate which type of cells enables researchers to turn an embryonic stem cell into any type of cell they need. In the case of schizophrenia, for example, researchers could generate schizophrenia-associated immune cells in the brain called microglia to

understand which gene variants contribute to the disease and might be suitable for therapeutic intervention.

Until now, discovering the transcription factors that could drive cell fate changes was a labor-intensive process with limited success. Zhang's team approached the challenge in a novel way: They created a library of over 3,500 plasmids, small circular DNA molecules that can be delivered into cells, in which each plasmid is barcoded and overexpresses one transcription factor in the human genome. They then pooled all these plasmids together and delivered them into embryonic stem cells and let the stem cells grow and differentiate. After this growth period, they analyzed the resulting types of cells that were created and sequenced the barcodes from the plasmids to determine which transcription factors led to which types of cells. Using this information, they then created a model to predict which combinations of transcription factors would produce the targeted cell types.

Using the library, which is available to researchers, Zhang's team showed that its contents can be combined with gene-editing technologies, which they pioneered,

Zhang's lab has generated a comprehensive library of transcription factors totaling over 3,500 plasmids, greatly accelerating scientists' ability to understand and study genetic variants underlying scores of diseases.

to create tailored cellular models of disease. Specifically, they first used gene-editing tools in stem cells to either knock out or overexpress the gene *DYRK1A*, which has been implicated in autism spectrum disorder and Down syndrome, and then they used a specific combination of transcription factors to create neurons. These neurons showed characteristics consistent with what was previously known about these diseases.

"Our library accelerates the ability of researchers worldwide to develop models to understand and study the genetic variants underlying scores of diseases," says Zhang. The availability of these models will accelerate efforts to identify potential therapeutic targets and reveal mechanistic insights into the molecular underpinnings of disease.

USING A CRISPR ACTIVATION SCREEN TO IDENTIFY GENES UNDERLYING DISEASE

Use of CRISPR extends far beyond genome editing. In 2022, Zhang's lab reported the first CRISPR activation screen to identify genes underlying resistance to immunotherapy in solid tumors. Immunotherapy for cancer requires harnessing cytotoxic T cells of the immune system to eliminate the cancer cells. Indeed, the therapy has transformed cancer treatment—but resistance to immunotherapy remains a major challenge.

To uncover the mechanisms driving immunotherapy resistance in the tumors, the researchers performed a genome-wide activation screen for genes that allow human melanoma cells to evade being killed by cytotoxic T cells. This type of screen calls for using the technology to express individual genes at higher levels than is typical. "Activation screens are the most powerful way that researchers have to learn what happens when a particular gene is turned on," says Zhang. The team identified four top candidate genes that conferred
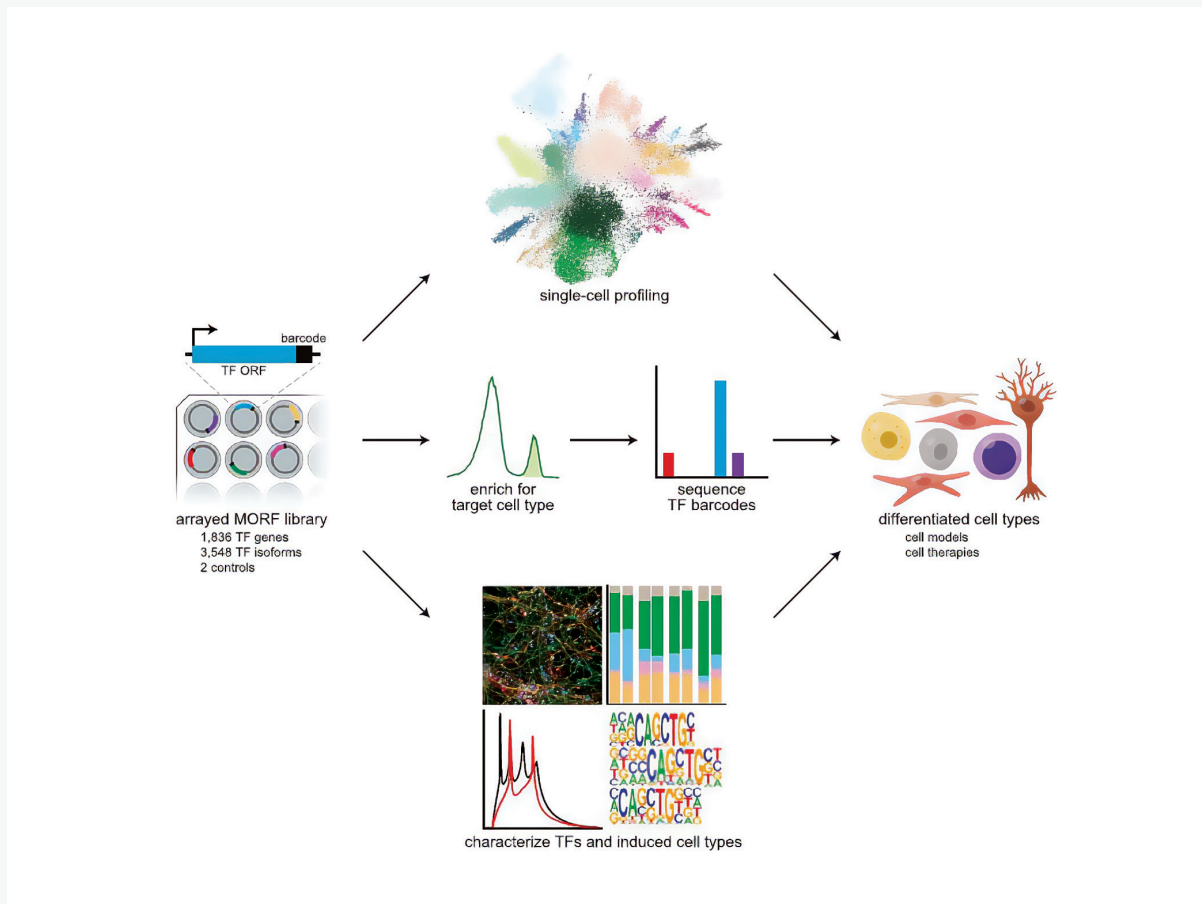
Transcription factors (TFs) are proteins that control which genes are turned on, and the set of genes turned on governs the type of cell that will result. The Zhang lab has now created a model to predict which combinations of TFs would produce targeted cell types. Image: Zhang lab

T cell resistance in diverse human cancer cells as well as in human tumor cells transplanted into immunocompromised mice.

This type of approach is particularly promising for identifying therapeutic targets because it reveals genes that contribute to disease when they are turned on higher than they would be in a healthy context. These "hyperactive" genes are in contrast to genes that contribute to disease when they are nonfunctional — in those cases, gene replacement is often the only choice, and that is a more difficult therapeutic approach. This study by Zhang's team paves the way for future CRISPR activation screens to identify hyperactive genes that may be involved in other diseases, including neuropsychiatric diseases.

Gene Therapy and Therapeutic Development

The labs of Poitras Center investigators Feng Zhang and Guoping Feng continue to crack open windows of discovery in the development of therapeutics to treat intractable psychiatric diseases.

Zhang, the James and Patricia Poitras Professor of Neuroscience, continues to develop new gene-modifying platforms drawn from systems in nature. Earlier, he pioneered the development of CRISPR-Cas9 as a genome-editing tool and its use in human cells. Today his team is transforming other molecules found in nature into next-generation therapeutics.

Feng, the James W. (1963) and Patricia T. Poitras Professor in Brain and Cognitive Sciences, and his team have made significant strides in developing gene therapy and animal models for treating complex brain disorders such as schizophrenia and autism spectrum disorder (ASD).

Here are some of their labs' recent advances.

Zhang lab: Driving a revolution in genome-editing technology

A PIPELINE TO MINE NEW MOLECULAR TOOLS

Zhang's team recently developed a computational pipeline to mine genomic and metagenomic sequences to identify ultrarare CRISPR-associated systems with the potential to be used as molecular tools. Using this pipeline, the researchers have identified dozens of RNA-guided systems that may form the basis of additional programmable DNA-modifying technologies.

"We are finding these incredible naturally existing machines that have been highly evolved for their own needs," says Zhang. "We're interested in engineering these systems to tweak them and adapt them for our needs—developing interventions to preserve human health."

A NEW CLASS OF DNA-CUTTING ENZYMES

The researchers recently discovered a new class of natural DNA-modifying systems called OMEGAs (Obligate Mobile Element Guided Activity), ancient DNA-cutting enzymes that originated in bacteria. They have engineered them to target and to cleave human cells. Each OMEGA has a small RNA encoded nearby that directs the enzyme to cut specific DNA sequences. The team named these RNAs "ωRNAs." OMEGAs are ideally suited for delivering cargo to cells, given their small size (about 30 percent the size of Cas9).

While the small size of the OMEGAs is a plus, they use relatively short RNA guides, which reduces their selectivity for targeted DNA sequences. So the Zhang team engineered the proteins and the RNA guides to improve the

robustness of the system and its specificity in targeting and cutting DNA. They have now generated an OMEGA that has activity on par with Cas9, and are further engineering it for precise DNA modulation, including turning off gene activity and editing genes. The next step is to test the engineered system in mouse models of disease.

A NATURAL WAY TO INSERT DNA SEQUENCES

Genetic elements called retrotransposons are small, repetitive DNA sequences that jump from one location in the genome to another, using RNA to "copy" themselves before jumping to a new location and converting the RNA into DNA and "pasting" the DNA into the new spot. Zhang researchers have been studying a retrotransposon in the silk moth called R2 to understand the molecular mechanism of this "copy and paste" route to inserting DNA sequences, a major outstanding goal in the gene-editing field. Led by Postdoctoral Fellow Max Wilkinson, they delineated the structure of the R2 protein in complex with the RNA template and target DNA insertion site. Using this structure, Wilkinson was able to define the parameters required for choosing the target insertion site and copying the R2 retrotransposon into it. Importantly, the researchers also showed that both the target site and the cargo sequence to be inserted can be reprogrammed. "We have developed many gene-editing tools over the past decade that perform different functions on DNA, but inserting large stretches of new DNA remains challenging," says Zhang. "R2 has naturally solved this challenge, and we are excited to learn from it and hopefully fill in this gap in the toolbox." They aim to engineer R2 so that it can copy an RNA sequence that will convert to the needed replacement gene and be targeted to a specific site in human cells.

PLATFORM THAT PACKAGES AND DELIVERS THERAPEUTICS

A powerful new modular platform made of a human protein called PEG10 that packages and delivers therapeutics to precise targets in the body promises to address the drawbacks of existing delivery modes: small cargo capacity, a tendency to provoke an immune response, and a propensity to accumulate in the liver and cause toxicity.
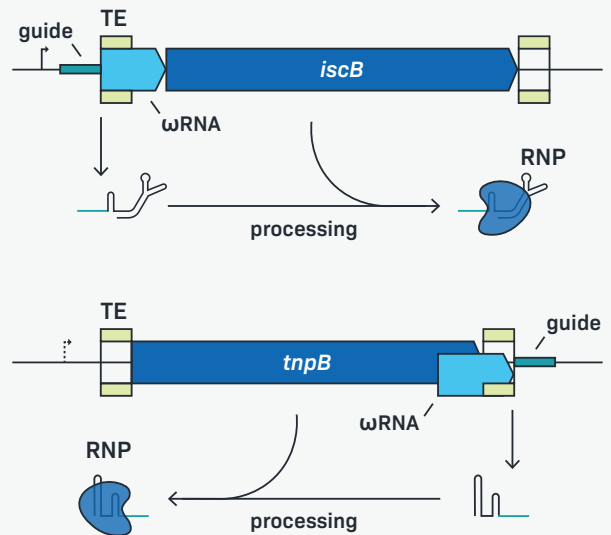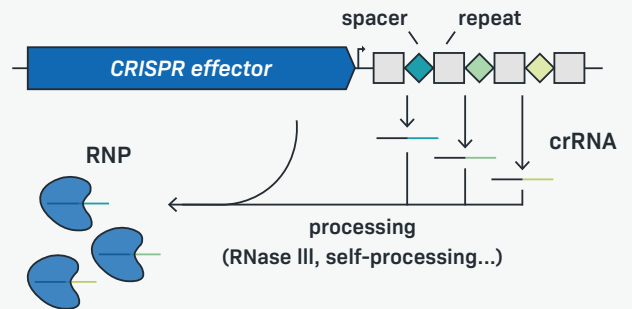
Comparison of OMEGA systems with other known RNA-guided systems. In contrast to CRISPR systems, which capture spacer sequences and store them in the locus within the CRISPR array, OMEGA systems may transpose their loci (or trans-acting loci) into target sequences, converting targets into ωRNA guides. Image courtesy of the researchers
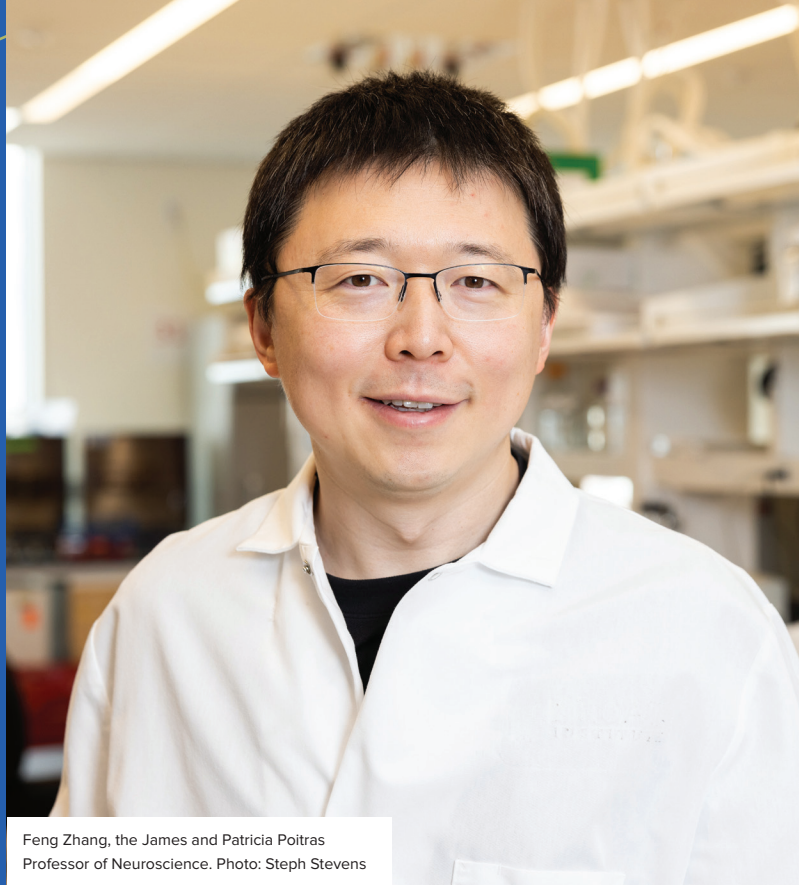
GENE THERAPY AND THERAPEUTIC DEVELOPMENT

> **We are finding these incredible naturally existing machines that have been highly evolved for their own needs. We're interested in engineering these systems and adapting them for our needs—developing interventions to preserve human health.**
>
> **–FENG ZHANG**

Feng Zhang, the James and Patricia Poitras Professor of Neuroscience. Photo: Steph Stevens

Called SEND (Selective Endogenous eNcapsidation for cellular Delivery), it relies on proteins like PEG10 that are produced in healthy human cells. PEG10 is derived from a "retroelement"—a fragment of a retrovirus that inserted itself into the genome of mammals millions of years ago. Over time, most retroelements are rendered nonfunctional, but some maintain virallike properties and have been adapted to serve roles in mammalian physiology. The Zhang lab was particularly interested in finding those retroelement-derived proteins in the human genome that maintained the ability to form a viruslike capsid, the shell that contains a virus's genetic information. "We thought, if these proteins are forming viruslike structures, maybe we can co-opt them and use them to package novel therapeutic information and deliver it to target cells," says Zhang.

Motivated by this goal, the Zhang team first confirmed that PEG10 forms a virallike capsid. But the PEG10 capsids went further, mirroring the capsid's ability to protect and package its own mRNA, which is then exported from the cell inside the capsids. By investigating this natural ability, they were able to then reprogram PEG10 to package an RNA of their design, called a cargoRNA, rather than its own mRNA. To target the delivery, they engineered

and attached fusogens to the capsid's exterior. They have since shown that SEND can successfully deliver cargoRNAs that encode and direct the CRISPR system, leading to precise gene editing in mammalian cells.

INJECTION SYSTEM COULD TRANSFORM GENE THERAPY

A natural bacterial system engineered by Zhang researchers has been shown to safely deliver a range of useful proteins—including ones for gene editing—to different mammalian cell lines as well as the brains of live mice. The team began with a tiny syringelike injection structure produced by a bacterium that naturally binds to insect cells and injects a payload into them.

"Delivery of therapeutic molecules into the right cells in the body is a major bottleneck for medicine," says Zhang. "By learning how nature transports proteins, we were able to develop a new platform that can help address this gap."

The syringes, called extracellular contractile injection systems (eCISs), consist of a rigid tube inside a sheath that contracts, driving a spike into the cell membrane. This forces protein cargo inside the tube to enter the cell. At

one end of the eCIS are tail fibers that recognize specific receptors on the cell surface and latch on. Previous research has shown that eCISs can naturally target insect and mouse cells, but graduate student Joseph Krietz has modified them to deliver proteins to human cells by reengineering the tail fibers to bind to different receptors.

The team has also used engineered eCISs to deliver cargos to cells, including base editor proteins (which can make single-letter changes to DNA) and proteins that are toxic to cancer cells.

Feng lab: Leaps forward in gene therapy, animal models for complex brain disorders

SUCCESS IN GENOME-ENGINEERING TECHNOLOGIES

In March 2022, the Feng lab launched the first-ever study of a gene-therapy treatment for a neurological disorder in nonhuman primates. The preliminary results have been very encouraging.

In 12 marmosets generated with a mutation in the *SHANK3* gene, which causes the neurodevelopmental disorder Phelan-McDermid syndrome, the researchers performed a wide range of behavioral tests before and after the gene therapy using an automated video tracking system to study social behavior, vocalizations, cognition, responses to stimuli, gait, and sleep quality compared to that of wild-type animals.

They investigated both early and late interventions: One group received the treatment at three months old, and another received it at nine months old. The treatment was an injection of the lab's healthy *SHANK3* "mini-gene," a gene reduced to its essential components delivered via a novel adeno-associated virus (AAV) capable of penetrating the blood-brain barrier.

All of the treated animals remained healthy after the therapy and did not show any adverse reactions. The team recorded more than 1,500 behavioral sessions to establish if the animals' behavior differed after the therapy. They found that except for one outlier, the gene-therapy group closely resembled typical wild-type animals, with most behavioral abnormalities improved. These included increased interest in social stimuli, better performance
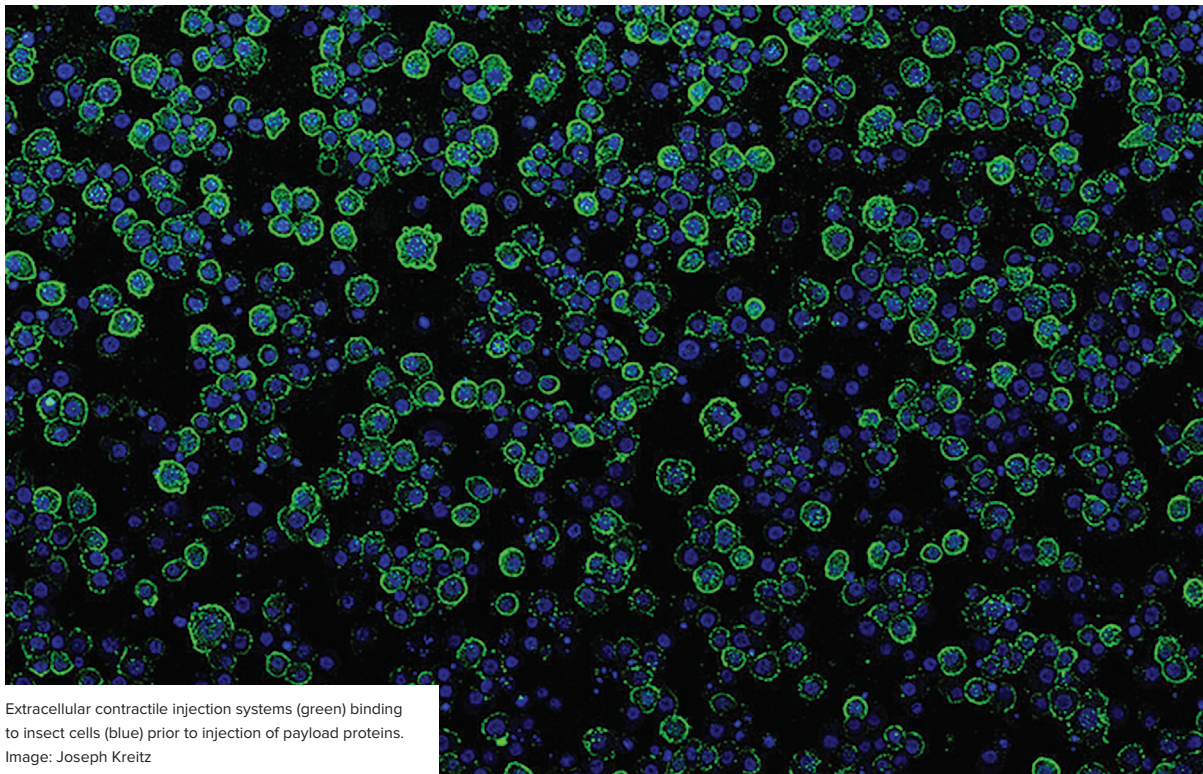
Extracellular contractile injection systems (green) binding to insect cells (blue) prior to injection of payload proteins.
Image: Joseph Kreitz

on cognitive tasks, and more typical social interactions. "These results give us the confidence to further develop our gene therapy for clinical applications in treating debilitating disorders," says Feng.

REFINING BASE-EDITING TOOLS

Feng's team has extended its investigation of gene therapy by employing base editing to correct the mutations in the *MECP2* gene, located on the X chromosome and the primary driver of the neurodevelopmental disorder Rett syndrome.

Rather than using CRISPR gene-editing tools to replace an entire dysfunctional gene with an intact copy, base editing makes "point" changes in individual DNA bases, either correcting or creating specific mutations, avoiding the possibility of off-target insertion of an entire gene.

Using a mouse model of Rett syndrome, the researchers targeted bases on a portion of the gene that is "a hot spot for mutations," including a recurrent mutation called R270X, says Postdoctoral Fellow Chenjie Shen. After adding the R270X mutation to the "hot spot," they used base editing to correct the mutation. The MECP2 protein was again produced at novel levels in most brain regions. Phenotypic issues in the mice were ameliorated, including obesity, impaired motor learning, and social deficits. The researchers are now screening additional RNA guides to target the treatment more precisely and generating marmoset models as the next step toward human trials.
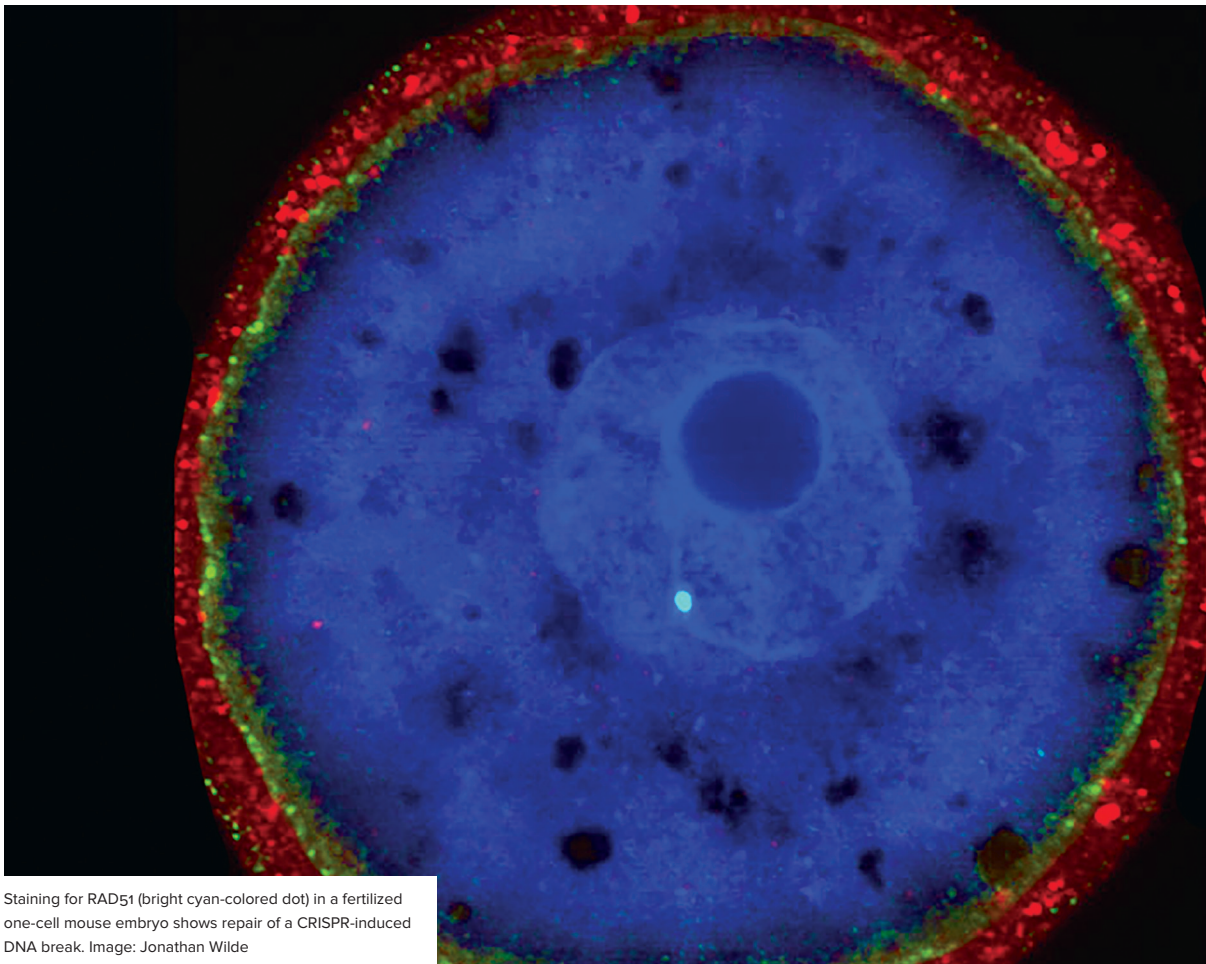
Staining for RAD51 (bright cyan-colored dot) in a fertilized one-cell mouse embryo shows repair of a CRISPR-induced DNA break. Image: Jonathan Wilde

> **Early results give us the confidence to further develop our gene therapy for clinical applications in treating debilitating disorders.**
>
> **—GUOPING FENG**

BREAKTHROUGH IN CORRECTING GENETIC MUTATIONS

Generating animal models of disease with gene-editing tools is painstaking and inefficient: Many of the treated embryonic cells don't incorporate an introduced gene mutation, and if they do, the change occurs in only one of the two gene copies in the cell — one from the father and one from the mother. To address the inefficiency, the Feng team tested whether adding a DNA repair protein called RAD51 to CRISPR gene-editing tools might improve the process. When they inserted RAD51 with a mutation in the gene *CHD2*, which is associated with autism, in mouse embryos, they found that a significantly higher percentage of the embryos carried the desired gene mutation on both chromosomes. Tests with a different gene yielded the same result.

RAD51's implications for gene therapy are enormous. The mechanism driving the enhanced gene editing is called interhomolog repair, whereby a DNA break on one chromosome is repaired using the gene on the second chromosome as the template. When they added RAD51 to a CRISPR tool programmed to cut the gene on one chromosome but did not include a replacement gene, they found that the CRISPR-targeted gene was edited to match the one on the uncut chromosome. "Our findings are the foundation for a new gene-therapy approach that could help solve problems with current approaches, including the risk of unwanted integration of replacement DNA throughout the genome," says Feng.

ADVANCES IN MODELS OF SCHIZOPHRENIA

Research has shown that mutations in 10 different genes strongly increase an individual's risk of developing schizophrenia. The Feng lab has been at the forefront of generating animal models of schizophrenia. The team's advances in this area include identifying the brain circuitry underlying delusions — a primary symptom of schizophrenia — using a mouse model carrying a mutation in the *GRIN2A* gene.

Advances extend to the development of a marmoset model carrying a mutation in the *SETD1A* gene to explore the mechanisms underlying deficits in schizophrenia including cognitive impairment, working memory deficits, and executive dysfunction. The researchers generated the gene mutation in marmoset embryos using prime editing. The technology enables precise, targeted editing of DNA using a CRISPR-Cas9 "nickase" to make a small "nick" on just one strand of DNA and then using an engineered protein to insert a large DNA sequence into the marked spot. Preimplantation genetic testing ensured that the mutation was present before embryo transfer. The lab now has one healthy *SETD1A* mutant marmoset and is generating more.

PEOPLE

Young researchers in the Poitras Center community describe what drives them to study psychiatric disorders and what they hope to accomplish.

Tamar Regev

2022–2024 Poitras Center
Postdoctoral Fellow,
Fedorenko Lab

Photo:
Steph Stevens

"I hope my research will lead to better treatments and quality of life for individuals with these disorders — and help us as a society to better understand and accept special populations."

Uncovering neural systems involved in auditory hallucinations

Tamar Regev, the 2022–2024 Poitras Center Postdoctoral Fellow, has identified a new neural system that may shed light on the auditory hallucinations experienced by patients diagnosed with schizophrenia.

"The system appears integral to prosody processing," says Regev. "'Prosody' can be described as the melody of speech—auditory gestures that we use when we're speaking to signal linguistic, emotional, and social information." The prosody processing system Regev has uncovered is distinct from the lower-level auditory speech processing system as well as the higher-level language processing system. Regev aims to understand how the prosody system, along with the speech and language processing systems, may be impaired in neuropsychiatric disorders such as schizophrenia, especially when experienced with auditory hallucinations in the form of speech.

"Knowing which neural systems are affected by schizophrenia can lay the groundwork for future research into interventions that target the mechanisms underlying symptoms such as hallucinations," says Regev. Passionate about bridging gaps between disciplines, she is collaborating with Ann Shinn, MD, MPH, of McLean Hospital's Schizophrenia and Bipolar Disorder Research Program.
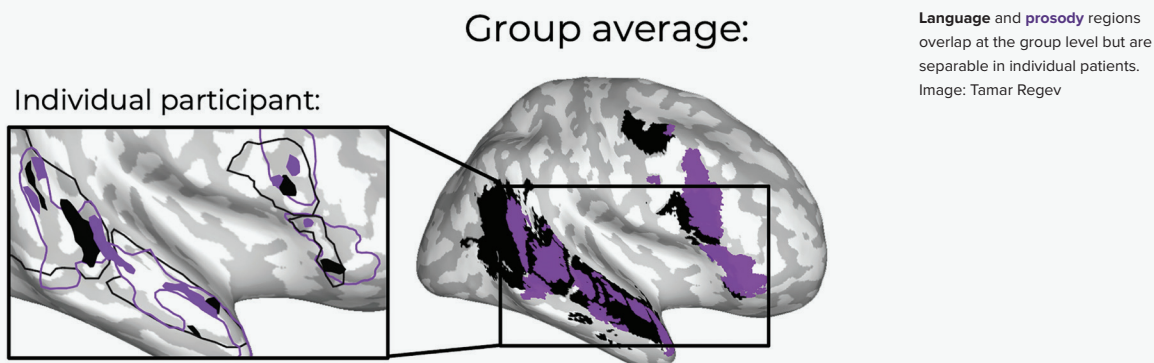
Regev's graduate work at the Hebrew University of Jerusalem focused on exploring the auditory system with electroencephalography (EEG), which measures electrical activity in the brain using small electrodes attached to the scalp. She came to MIT to study under Evelina Fedorenko, a world leader in researching the cognitive and neural mechanisms underlying language processing. With Fedorenko she has learned to use functional magnetic resonance imaging (fMRI), which reveals the brain's functional anatomy by measuring small changes in blood flow that occur with brain activity.

"EEG has very good temporal resolution but poor spatial resolution, while fMRI provides a map of the brain showing where neural signals are coming from," says Regev. "With fMRI I can connect my work on the auditory system with that on the language system."

Regev developed a unique fMRI paradigm to do that. While her human subjects are in the scanner, she is comparing brain responses to speech with expressive prosody versus flat prosody to find the role of the prosody system among the auditory, speech, and language regions. She plans to apply her findings to analyze a rich data set drawn from fMRI studies that Fedorenko and Shinn began a few years ago while investigating the neural basis of auditory hallucinations in patients with schizophrenia and bipolar disorder. Regev is exploring how the neural architecture may differ between control subjects and those with and without auditory hallucinations as well as those with schizophrenia and bipolar disorder.

"This is the first time these questions are being asked using the individual-subject approach developed in the Fedorenko lab," says Regev. The approach provides superior sensitivity, functional resolution, interpretability, and versatility compared with the group analyses of the past. "I hope my research will lead to better treatments and quality of life for individuals with these disorders—and help us as a society to better understand and accept special populations."

Individual participant:

Group average:

Language and **prosody** regions overlap at the group level but are separable in individual patients. Image: Tamar Regev

Tingting Zhou

Postdoctoral Fellow,
Feng Lab

Photo:
Steph Stevens

"Today's antipsychotics can control some symptoms but can't cure the underlying condition. Attacking schizophrenia at the circuit level can."

An integrative approach to schizophrenia

Tingting Zhou, a postdoctoral fellow in the lab of Guoping Feng, is committed to fully understanding the pathology of schizophrenia, from its symptoms to its biological drivers. That deep knowledge, she says, "is necessary to develop a novel therapeutic approach that can truly improve the quality of schizophrenic patients' lives."

Zhou has already made breakthroughs in that direction.

She completed her graduate work at the Institute of Neuroscience, Chinese Academy of Sciences, and Zhejiang University School of Medicine, where she primarily studied the neural circuits of social dominance behaviors. As her research interests gravitated toward schizophrenia, she saw that the lack of animal models of the disease was significantly hampering both research and clinical progress.

She came to MIT to study under Feng — an expert in generating animal models of psychiatric disorders — to help change that. Her unique "integrated" research approach accelerates the path to new therapeutics by connecting computational findings from behavioral research with human patients to her own basic-science studies with animals.

"Just looking at the biological changes in the brain of an animal genetically engineered to have a psychiatric disease does not really connect to human symptoms," Zhou says. "I wanted to link that 'top-down' human research with my 'bottom-up' animal-model research."

To do so, she worked with gene-editing experts in the Feng lab to generate a mouse model carrying a genetic mutation identified in schizophrenia patients (in the *GRIN2A* gene). She also developed a unique lever-pressing reward-based behavioral task to study delusions — a primary symptom of schizophrenia — in the animals.

Delusions result from a deficit in the ability to "update beliefs in a dynamically changing environment," says Zhou. Her behavioral task showed the same deficit to be true for the mutant mice. To plumb the biological mechanism underlying their impaired behavior, Zhou turned to imaging studies of human patients and saw a weakened connectivity between two brain regions: the
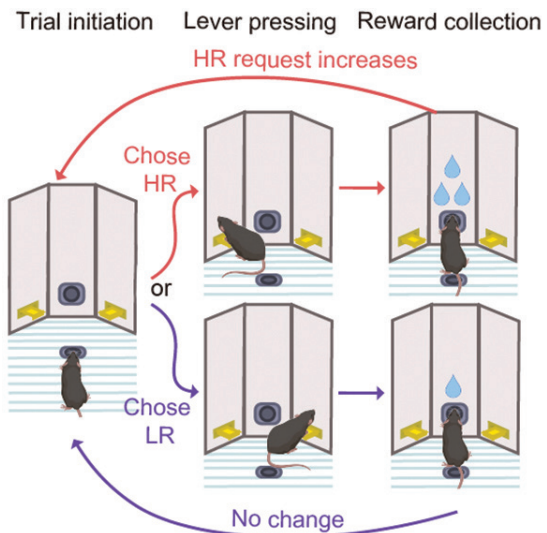
Schematic diagram of high-reward (HR)/low-reward (LR) lever-pressing task, designed by Zhou, to model the belief-updating process in mice. Image: Tingting Zhou

thalamus and the prefrontal cortex. Follow-up studies inhibiting thalamus activity in the control mice, boosting the thalamus-prefrontal connectivity in the mutant mice, and directly examining the thalamus-prefrontal neuronal circuit in the mutant mice provided further evidence of the circuit as mediator of the behavior.

"We can see that boosting this connectivity can correct the behavior in the mouse model for schizophrenia," says Zhou. "This will potentially provide us with a target for novel therapeutic approaches for human patients."

Schizophrenia is a complicated disorder with multiple symptoms, ranging from hallucinations to disordered speech, and multiple implicated genes. Research has shown that mutations in 10 different genes strongly increase an individual's risk of developing the disease. Zhou is using a few mouse models with some of those 10 high-risk genes. She is currently evaluating the behavior of the mouse models and using functional ultrasound imaging to scan their brains to see whether the behavioral deficits converge with specific neural circuit alterations. Finding common circuits for different high-risk genes could revolutionize the treatment of the disease.

"Today's antipsychotics can control some symptoms but can't cure the underlying condition," she says. "Attacking schizophrenia at the circuit level can."

Sadie Zacharek

*Graduate Student,
Gabrieli Lab*

Photo:
Steph Stevens

"John Gabrieli and I are eager to explore how we might use neuroimaging as a step toward personalized medicine."

Neuroimaging as a window into treatment response

From summer internships as an undergraduate studying neuroscience at the University of Notre Dame, Sadie Zacharek developed interests in areas ranging from neuroimaging to developmental psychopathologies, from basic-science research to clinical translation. When she interviewed with John Gabrieli, the Grover Hermann Professor of Health Sciences and Technology and Cognitive Neuroscience, for a position in his lab as a graduate fellow, everything came together.

"The brain provides a window not only into dysfunction but also into response to treatment," she says. "John and I both wanted to explore how we might use neuroimaging as a step toward personalized medicine."

Zacharek joined the Gabrieli lab in 2020. There, she has been designing and helping launch studies focusing on the neural mechanisms driving childhood depression and social anxiety disorder with the aim of developing strategies to predict which treatments will be most effective for individual patients.

Helping children and adults

"Depression in children is hugely understudied," says Zacharek. "Most of the research has focused on adult and adolescent depression." But the clinical presentation differs in the two groups, she says. "In children, irritability can be the primary presenting symptom rather than melancholy."

To get to the root of childhood depression, she is exploring both the brain basis of the disorder and how the parent-child relationship might influence symptoms. "Parents help children develop their emotion-regulation skills," she says. "Knowing the underlying mechanisms could, in family-focused therapy, help them turn a 'downward spiral' into irritability, into an 'upward spiral,' away from it."

The studies she is conducting include functional magnetic resonance imaging (fMRI) of children to explore their brain responses to positive and negative stimuli, fMRI of both the child and parent to compare maps of their brains' functional connectivity, and magnetic resonance spectroscopy to explore the neurochemical environment of both, including quantities of neurometabolites that indicate inflammation (higher levels have been found to correlate with depressive pathology).

"If we could find a normative range for neurochemicals and then see how far someone has deviated in depression, or a neural signature of elevated activity in a brain region, that could serve as a biomarker for future interventions," she says. "Such a biomarker would be especially relevant for children given that they are less able to articulately convey their symptoms or internal experience."

Social anxiety disorder is a chronic and disabling condition that affects about 7.1 percent of U.S. adults. Treatment usually involves cognitive behavior therapy (CBT), and then, if there is limited response, the addition of a selective serotonin reuptake inhibitor (SSRI), as an anxiolytic. But what if research could reveal the key neurocircuitry of social anxiety disorder as well as changes associated with treatment? That could open the door to predicting treatment outcome.

Zacharek is collecting neuroimaging data, as well as clinical assessments, from participants. The participants diagnosed with social anxiety disorder will then undergo 12 weeks of group CBT, followed by more data collection, and then individual CBT for 12 weeks plus an SSRI for those who do not benefit from the group CBT. The results from those two time points will help determine the best treatment for each person.

"We hope to build a predictive model that could enable clinicians to scan a new patient and select the optimal treatment," says Zacharek. "John's many long-standing relationships with clinicians in this area make all of these translational studies possible."

A sagittal view of an anatomical MRI scan of Sadie's brain. Image: Sadie Zacharek
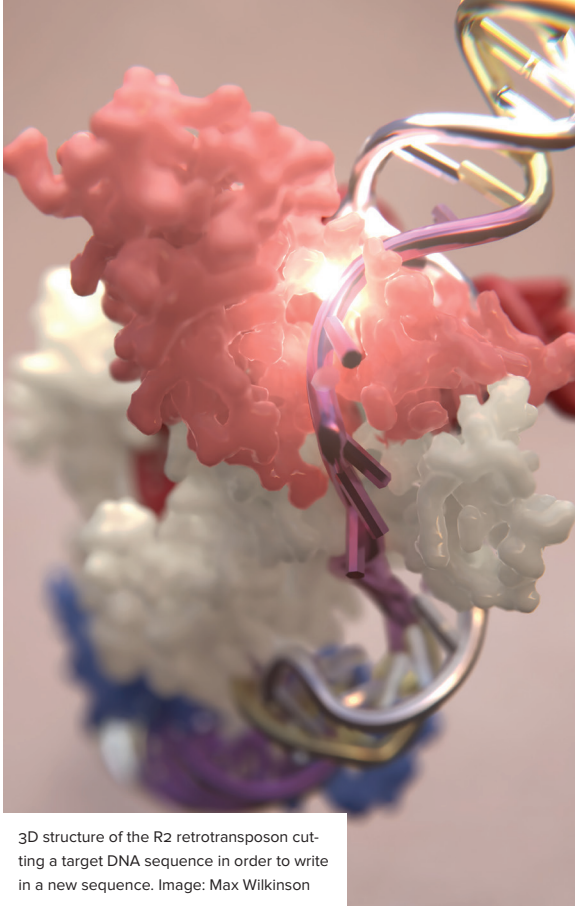
Max Wilkinson

*Postdoctoral Fellow,
Zhang Lab*

Photo:
Steph Stevens

"In addition to doing research I'm passionate about, I'm gaining wisdom from people with an incredible range of expertise."

3D structure of the R2 retrotransposon cutting a target DNA sequence in order to write in a new sequence. Image: Max Wilkinson

A "copy and paste" strategy for gene therapy

In the spring of 2019, Max Wilkinson, then a graduate student at Cambridge University, stood at the podium of the Cold Spring Harbor Laboratory Symposium "RNA Control & Regulation" and presented research he'd done in the lab of Kiyoshi Nagai on the spliceosome, a "huge molecular machine," he says, that excises "introns" — long nonprotein coding DNA sequences — from genes while they are copied into messenger RNA.

It was groundbreaking work, made possible by Wilkinson's use of electron cryomicroscopy, a revolutionary type of electron microscopy applied to samples cooled to −180° Celsius that shows the three-dimensional biological processes of proteins in atomic detail. The other 54 presenters were principal investigators, giants in their fields from around the world. Feng Zhang, the James and Patricia Poitras Professor in Neuroscience, was among them. Rhiannon Macrae, Zhang's scientific advisor, was in the audience and approached Wilkinson.

"I was impressed with his talk and tried to recruit him!" says Macrae.

Zhang was impressed, too. "Feng was very keen to start using electron cryomicroscopy, and I had experience with it, having worked in an institution that helped develop it," says Wilkinson, who has been a postdoctoral fellow in Zhang's lab since August 2021.

Getting "under the hood" of proteins

A native of New Zealand, Wilkinson earned his BSc in biochemistry at the University of Otago. There he was introduced to structural biology. "It only takes one good lecture to get you hooked on something, and it was a lecture on structural biology for me," he says. "I love understanding how proteins work. They are basically tiny machines. If you don't have a clear picture of how a machine looks, it's difficult to understand how it works."

In the Zhang lab, Wilkinson is exploring the structure of retrotransposons. Transposons are repetitive DNA sequences that jump from one location in the genome to another. They have played a significant role in the evolution of genomes of many species, including humans. Retrotransposons are similar but, says Wilkinson, "they have an RNA intermediate." They too move locations, but they use RNA to make a copy of themselves before jumping to a new location and converting the RNA into DNA. "With a retrotransposon, the original copy is preserved. You could call the behavior of transposons 'cut and paste' and of retrotransposons 'copy and paste.'"

Scientists believe that retrotransposons may be involved in neuron development. Wilkinson has focused on a retrotransposon in the silk worm as a proxy for its version in humans. Studying the structure and behavior of this retrotransposon could lead to advances in gene therapy, particularly in neurons. The retrotransposon would have to be programmed both to recognize a specific DNA site to "jump" to and to copy an RNA sequence that would convert to the appropriate gene to be "pasted" into the genome. It would also have to be paired with a CRISPR tool to make the cut for the new gene.

Wilkinson is grateful to be part of Zhang's diverse team. "People are doing genome editing, gene-therapy delivery methods — things I've never encountered before," he says. "In addition to doing research I'm passionate about, I'm gaining wisdom from people with an incredible range of expertise."

SCIENTIFIC PUBLICATIONS

Peer-reviewed research generated by the Poitras Center amplifies bold new ideas and insights into psychiatric illness.

Scientific Publications

Scientists in the Poitras Center for Psychiatric Disorders Research continue to generate powerful insights into the biological and genetic bases of major mental illness and to advance novel therapeutic approaches. Sharing their groundbreaking findings with others in the research and clinical practice communities — and broader society — through peer-reviewed journals is essential to cultivating bold ideas and initiating promising collaborations. Following is a summary of the center's scientific papers from summer 2021 to summer 2023.

Fanzor is a eukaryotic programmable RNA-guided endonuclease.

Saito M, Xu P, Faure G, Maguire S, Kannan S, Altae-Tran H, Vo S, Desimone A, Macrae RK, **Zhang F**. | *Nature* (Jun 2023)

Zhang lab scientists uncovered the first programmable RNA-guided system in eukaryotes and showed how it can be reprogrammed for applications in human genome engineering.

Cryo-EM structure of the transposon-associated TnpB enzyme.

Nakagawa R, Hirano H, Omura SN, Nety S, Kannan S, Altae-Tran H, Yao X, Sakaguchi Y, Ohira T, Wu WY, Nakayama H, Shuto Y, Tanaka T, Sano FK, Kusakizako T, Kise Y, Itoh Y, Dohmae N, van der Oost J, Suzuki T, **Zhang F**, Nureki O. | *Nature* (Apr 2023)

Scientists from the Zhang lab and the University of Tokyo used cryo-electron microscopy to reveal the unexpected architecture of Cas12 transposon-associated TnpB proteins, demonstrating how TnpB recognizes RNA and cleaves target DNA complementary to the guide. The findings provide mechanistic insights into TnpB function and advance our understanding of the evolution from transposon-encoded TnpB proteins to CRISPR-Cas12 effectors.
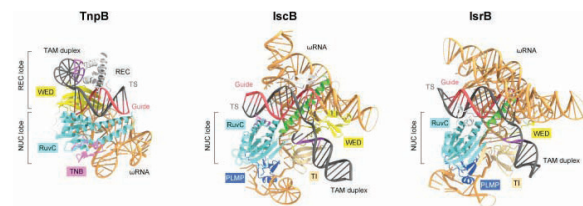
Structural comparison of the TnpB protein with IscB (from the human gut metagenome) and IsrB (from *Desulfovirgula thermocuniculi*). Image: Nakagawa et al. From "Extended Data Fig. 10" at www.ncbi.nlm.nih.gov/pmc/articles/PMC10097598/

Monosynaptic restriction of the antero-grade herpes simplex virus strain H129 for neural circuit tracing.

Fischer KB, Collins HK, Pang Y, Roy DS, Zhang Y, **Feng G**, Li SJ, Kepecs A, Callaway EM. | *J Comp Neurol* (Apr 2023)

Using an adeno-associated virus combined with Herpes Simplex Virus 1 strain H129, the authors designed a novel tracing system that labels postsynaptic cells across the entire brain. This molecular tool has the promise to be useful in systems neuroscience research.

Programmable protein delivery with a bacterial contractile injection system.

Kreitz J, Friedrich MJ, Guru A, Lash B, Saito M, Macrae RK, **Zhang F**. | *Nature* (Apr 2023)

Extracellular contractile injection systems (eCISs) are syringelike complexes that inject proteins into cells by driving a spike through the cellular membrane. A team led by Feng Zhang showed that an eCIS derived from the bacterium *Photorhabdus asymbiotica* can be reprogrammed to target human cells with efficiencies approaching 100 percent. They demonstrated that this eCIS can deliver diverse protein payloads — including Cas9 and base editors for gene therapy and toxins to cancerous cells, opening up the possibility of targeting delivery specifically to the cell types of interest.

Structure of the R2 non-LTR retrotransposon initiating target-primed reverse transcription.

Wilkinson ME, Frangieh CJ, Macrae RK, **Zhang F**. | *Science* (Apr 2023)

Non-long terminal repeat retrotransposons are an abundant class of eukaryotic transposons that insert into genomes by target-primed reverse transcription. Researchers report on the cryo-electron microscopy structure of the *Bombyx mori* retrotransposon and demonstrate use of Cas9 to retarget R2 in vitro to non-native sequences, suggesting future use as a reprogrammable RNA-based gene-insertion tool.

Are language features associated with psychosis risk universal? A study in Mandarin-speaking youths at clinical high risk for psychosis.

Agurto C, Norel R, Wen B, Wei Y, Zhang D, Bilgrami Z, Hsi X, Zhang T, Pasternak O, Li H, Keshavan M, Seidman LJ, **Whitfield-Gabrieli S**, Shenton ME, Niznikiewicz MA, Wang J, Cecchi G, Corcoran C, Stone WS. | *World Psychiatry* (Feb 2023)

Natural language processing analyses show decreased coherence and complexity in the speech of individuals with schizophrenia and at high risk for psychosis. It has remained unknown, however, whether such findings generalize to languages other than English. This study is the first to use natural language processing and acoustic analyses to characterize speech among Mandarin speakers at high risk for psychosis. Findings support the idea of universal features of speech disturbance across psychosis, particularly reduced coherence, word usage, and pause behavior.

Cerebello-cerebral functional connectivity networks in major depressive disorder: a CAN-BIND-1 study report.

Anteraper SA, Guell X, Lee YJ, Raya J, Demchenko I, Churchill NW, Frey BN, Hassel S, Lam RW, MacQueen GM, Milev R, Schweizer TA, Strother SC, **Whitfield-Gabrieli S**, Kennedy SH, Bhat V; CAN-BIND Investigator Team. | *Cerebellum* (Feb 2023)

This resting-state functional MRI study aimed to delineate the role of cerebellar functional networks in depression. In comparison to healthy controls, participants with major depressive disorder displayed increased connectivity within the cerebello-cerebral default mode network. Findings confirm previously reported associations between major depressive disorder, default mode network, and the cerebellum, and highlight the role of these locations for the development of imaging-based biomarkers and targets for neuromodulation therapies.
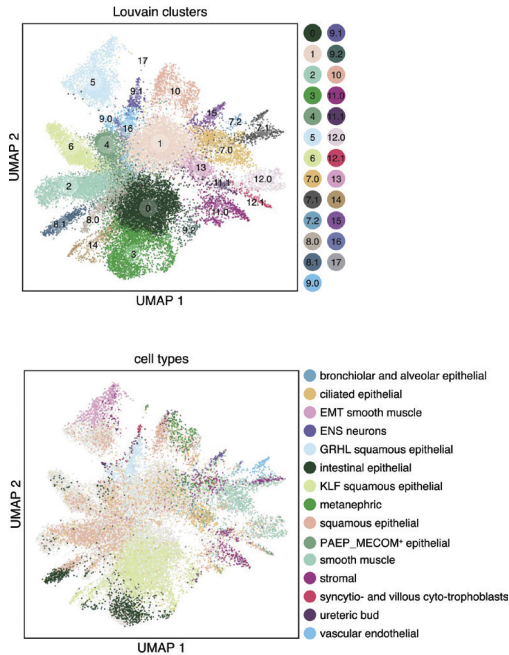
Uniform manifold approximation and projection of scRNA-seq data from 28,825 differentiated cells. The colors indicate Louvain clusters (top) and nominated reference cell types with score >0.3 (bottom). Image: Joung et al. From ars.els-cdn.com/content/image/1-s2.0-S0092867422014702-gr3_lrg.jpg

A transcription factor atlas of directed differentiation.

Joung J, Ma S, Tay T, Geiger-Schuller KR, Kirchgatterer PC, Verdine VK, Guo B, Arias-Garcia MA, Allen WE, Singh A, Kuksenko O, Abudayyeh OO, Gootenberg JS, Fu Z, Macrae RK, Buenrostro JD, Regev A, **Zhang F**. | *Cell* (Jan 2023)

Transcription factors regulate gene programs and control diverse cellular processes and cell states. To better understand transcription factors and the programs they control, members of the Zhang laboratory created a barcoded library of more than 3,500 annotated human transcription factor splice isoforms, mapped expression profiles to known cell types, and validated combinations of transcription factors that can induce differentiation into desired cell types. Further, they developed a strategy for predicting combinations of transcription factors that produce target expression profiles matching a wide range of reference cell types to accelerate engineering of specific cell replacement therapies.

Can machine learning identify childhood characteristics that predict future development of bipolar disorder a decade later?

Uchida M, Bukhari Q, DiSalvo M, Green A, Serra G, Hutt Vater C, Ghosh SS, Faraone SV, **Gabrieli JDE**, Biederman J. | *J Psychiatr Res* (Dec 2022)

This study, led by Gabrieli and Biederman, examined whether bipolar disorder can be predicted using clinical data and machine-learning algorithms. In addition to sociodemographic data, children were assessed with psychometric scales, structured diagnostic interviews, and cognitive and social functioning assessments. The team developed a machine-learning algorithm that predicted bipolar disorder with 75 percent sensitivity and 76 percent specificity. These results can help psychiatrists more rapidly zero in on the best medication choices for patients with bipolar disorder.

RNA-activated protein cleavage with a CRISPR-associated endopeptidase.

Strecker J, Demircioglu FE, Li D, Faure G, Wilkinson ME, Gootenberg JS, Abudayyeh OO, Nishimasu H, Macrae RK, **Zhang F**. | *Science* (Nov 2022)

In this paper, Zhang and team determine the protein substrate, structure, and mechanism of a CRISPR-associated protease from the marine organism *Desulfonema ishimotonii*, reveal its natural function in coordinating a transcriptional response to foreign genetic material, and engineer it for novel RNA-sensing applications in vitro and in human cells.

Structure of the IscB-ωRNA ribonucleo-protein complex, the likely ancestor of CRISPR-Cas9.

Kato K, Okazaki S, Kannan S, Altae-Tran H, Demircioglu FE, Isayama Y, Ishikawa J, Fukuda M, Macrae RK, Nishizawa T, Makarova KS, Koonin EV, **Zhang F**, Nishimasu H. | *Nat Commun* (Nov 2022)

Transposon-encoded IscB family proteins are RNA-guided nucleases in the system, and likely ancestors of the RNA-guided nuclease Cas9 protein. Here, researchers report the cryo-electron microscopy structure of an IscB protein from the human gut metagenome. These findings provide insights into the mechanism of the programmable DNA cleavage by the IscB-ωRNA complex and the evolution of type II CRISPR-Cas9 effector complexes.

Big contributions of the little brain for precision psychiatry.

Anteraper S, Guell X, **Whitfield-Gabrieli S**. | *Front Psychiatry* (Oct 2022)

Previous work using 3T functional MRI parcellated the human dentate nuclei, the primary output of the cerebellum, to three distinct zones contributing to default-mode, salience-motor, and visual brain networks. In this piece, the authors highlight the possibility of targeting specific functional territories within the cerebellum using noninvasive brain stimulation, potentially leading to the refinement of cerebellar-based therapeutics for precision psychiatry.

Microfluidic enrichment and computational analysis of rare sequences from mixed genomic samples for metagenomic mining.

Cui N, Faure G, Singh A, Macrae R, **Zhang F**. | *CRISPR J* (Oct 2022)

Many powerful molecular biology tools have their origins in natural systems, including the CRISPR effectors Cas9, Cas12, and Cas13. To accelerate metagenomic mining and reveal other CRISPR systems and natural systems with novel mechanisms, the Zhang team developed a high-throughput, low-cost droplet microfluidic-based method for enrichment of rare sequences. Using a computational pipeline, they searched for the presence of CRISPR-Cas systems, identifying a previously unknown system that may be useful in biomedical applications.

Structure of the OMEGA nickase IsrB in complex with ωRNA and target DNA.

Hirano S, Kappel K, Altae-Tran H, Faure G, Wilkinson ME, Kannan S, Demircioglu FE, Yan R, Shiozaki M, Yu Z, Makarova KS, Koonin EV, Macrae RK, **Zhang F**. | *Nature* (Oct 2022)

RNA-guided systems, such as CRISPR-Cas, combine programmable substrate recognition with enzymatic function. Zhang and colleagues identified a new class of RNA-guided systems, termed OMEGA, which include IscB (the likely ancestor of Cas9) and the nickase IsrB, a homologue of IscB. Here, they report on the structure of *Desulfovirgula thermocuniculi* IsrB as well as comparisons to other RNA-guided systems, advancing our understanding of the biology and evolution of these diverse systems.

Structure and engineering of the minimal type VI CRISPR-Cas13bt3.

Nakagawa R, Kannan S, Altae-Tran H, Takeda SN, Tomita A, Hirano H, Kusakizako T, Nishizawa T, Yamashita K, **Zhang F**, Nishimasu H, Nureki O. | *Mol Cell* (Sept 2022)

CRISPR-Cas13 effector enzymes catalyze RNA-guided RNA cleavage and have been harnessed for various technologies, such as RNA detection, targeting, and editing. Here, researchers report on the structures of the Cas13bt3-guide RNA complex and establish rationally engineered enhanced Cas13bt3 variants and ultra-compact RNA base editors. This study improves our mechanistic understanding of CRISPR-Cas13 enzymes and paves the way for the development of efficient Cas13-mediated technologies.

Dynamic intervention-based biomarkers may reduce heterogeneity and motivate targeted interventions in clinical high risk for psychosis.

Niznikiewicz MA, Brady RO, **Whitfield-Gabrieli S**, Keshavan MS, Zhang T, Li H, Pasternak O, Shenton ME, Wang J, Stone WS. | *Schizophr Res* (Aug 2022)

Based on their studies of individuals at clinical high-risk states for psychosis, the Shanghai-at-Risk-for-Psychosis team developed a mechanistic approach to identify and manipulate neural networks involved in schizophrenia. This novel methodology utilizes brain responses to targeted manipulations of specific neural networks as putative biomarkers that will provide foundations for intervention-based models.
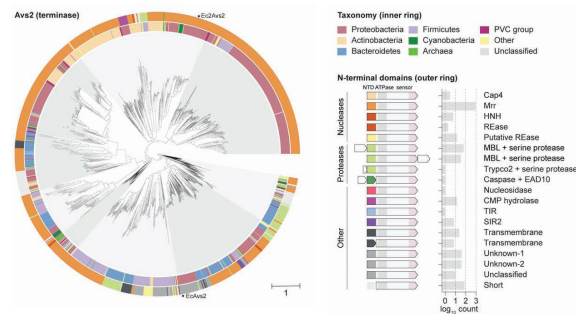
Maximum likelihood tree of representatives of the ATPase-2 group of enzymes. Image: Gao et al. Figure 6 from www.ncbi.nlm.nih.gov/pmc/articles/PMC10028730/#ABS3title

Prokaryotic innate immunity through pattern recognition of conserved viral proteins.

Gao LA, Wilkinson ME, Strecker J, Makarova KS, Macrae RK, Koonin EV, **Zhang F**. | *Science* (Aug 2022)

Organisms have evolved numerous defense mechanisms against viral infections including, in animals, plants, and fungi, proteins that can bind to structural features of viruses and, in response, activate defense mechanisms. In this paper, the Zhang team show that a similar immune system exists in prokaryotes, allowing these single-celled organisms to detect and destroy viruses that infect them.

Anterior thalamic circuits crucial for working memory.

Roy DS, Zhang Y, Aida T, Shen C, Skaggs KM, Hou Y, Fleishman M, Mosto O, Weninger A, **Feng G**. | *Proc Natl Acad Sci USA* (May 2022)

Alterations in the structure and functional connectivity of anterior thalamic nuclei have been linked to reduced cognition during aging; however, specific circuits that contribute to higher cognitive functions remain understudied. A team led by Guoping Feng found that the anteroventral subdivision of anterior thalamic nuclei is necessary specifically during the maintenance phase of a spatial working memory task.
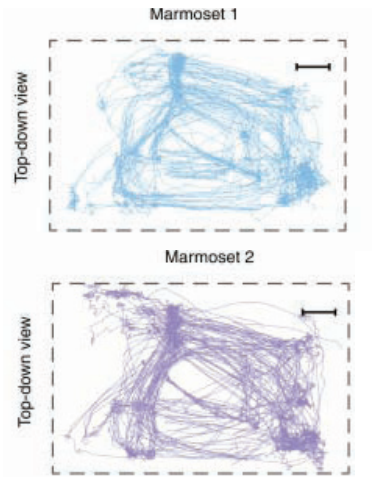
DeepLabCut is now being applied to track social behaviors of multiple marmosets. These tracks show 30 minutes of activity plotted from two marmosets. Image: Lauer et al. Figure 5 from www.ncbi.nlm.nih.gov/pmc/articles/PMC9007739/

Multi-animal pose estimation, identification and tracking with DeepLabCut.

Lauer J, Zhou M, Ye S, Menegas W, Schneider S, Nath T, Rahman MM, Di Santo V, Soberanes D, **Feng G**, Murthy VN, Lauder G, Dulac C, Mathis MW, Mathis A. | *Nat Methods* (Apr 2022)

Estimating the pose of multiple animals is a challenging computer vision problem. To take up this challenge, a team of researchers from the Feng lab, Swiss Federal Institute of Technology, and other institutions built on DeepLabCut, an open-source pose estimation toolbox, and provided high-performance animal assembly and tracking features required for multi-animal scenarios.

Mapping genomic loci implicates genes and synaptic biology in schizophrenia.

Trubetskoy V, Pardiñas AF, et al.; Schizophrenia Working Group of the Psychiatric Genomics Consortium. | *Nature* (Apr 2022)

Schizophrenia has a heritability of 60-80 percent, much of which is attributable to common risk alleles. In a genome-wide association study of 76,755 individuals with schizophrenia and 243,649 control individuals, a global team of scientists including Guoping Feng reported common variant associations at 287 distinct genomic loci. Using fine-mapping and functional genomic data, they identified 120 genes likely to underpin associations at some of these loci.

Altered working memory-related brain activity in children at familial high risk for psychosis: A preliminary study.

van Gool KCA, Collin G, Bauer CCC, Molokotos E, Mesholam-Gately RI, Thermenos HW, Seidman LJ, **Gabrieli JDE**, **Whitfield-Gabrieli S**, Keshavan MS. | *Schizophr Res* (Feb 2022)

Schizophrenia is a heritable illness that usually manifests in early adulthood but is increasingly viewed as a neuro-developmental disorder. This study of children ages 7-12 provided preliminary evidence that altered brain activity and impaired working memory function during working memory tasks are already present in preadolescent children at familial high risk for psychosis.
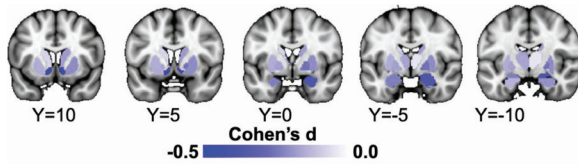
fMRI scans reveal that relative to healthy adolescents, depressed-anxious adolescents show reduced brain volume in several subcortical regions. Image: Auerbach et al. Figure 1 from www.ncbi.nlm.nih.gov/pmc/articles/PMC8643367/?report=reader

Reward-related neural circuitry in depressed and anxious adolescents: A Human Connectome Project.

Auerbach RP, Pagliaccio D, Hubbard NA, Frosch I, Kremens R, Cosby E, Jones R, Siless V, Lo N, Henin A, Hofmann SG, **Gabrieli JDE**, Yendiki A, **Whitfield-Gabrieli S**, Pizzagalli DA. | *J Am Acad Child Adolesc Psychiatry* (Feb 2022)

In this brain imaging study, researchers leading the Boston Adolescent Neuroimaging of Depression and Anxiety Human Connectome Project tested subcortical volume and nucleus accumbens activation during an incentive processing task among 14- to 17-year-olds with a depressive and/or anxiety disorder. Relative to healthy youth, depressed and/or anxious adolescents exhibited reduced nucleus accumbens volume and activation following receipt of a reward.

UG/Abi: a highly diverse family of prokaryotic reverse transcriptases associated with defense functions.

Mestre MR, Gao LA, Shah SA, López-Beltrán A, González-Delgado A, Martínez-Abarca F, Iranzo J, Redrejo-Rodríguez M, **Zhang F**, Toro N. | *Nucleic Acids Res* (Jun 2022)

Reverse transcriptases are enzymes capable of synthesizing DNA using RNA as a template. In this work, scientists analyzed and classified previously unknown reverse transcriptases, highlighting the presence of one of these systems in novel families of human gut viruses. This work lays the foundation for a comprehensive understanding of highly diverse enzymes with enormous biotechnology potential.

Convergence, preliminary findings and future directions across the four human connectome projects investigating mood and anxiety disorders.

Tozzi L, Anene ET, Gotlib IH, Wintermark M, Kerr AB, Wu H, Seok D, Narr KL, Sheline YI, **Whitfield-Gabrieli S**, Williams LM. | *Neuroimage* (Dec 2021)

In this paper, researchers highlighted preliminary results of the four Connectome Studies Related to Human Disease investigating mood and anxiety disorders. The projects used comparable and standardized Human Connectome Project MRI protocols and integrated clinical and neuropsychological assessments, demographic information, clinical diagnoses, symptoms of mood and anxiety disorders, cognitive function, and exposure to early life stress. Taken together, the data reported by the studies describe a rich constellation of convergent biological, clinical, and behavioral phenotypes that span the peak ages for the onset of emotional disorders.
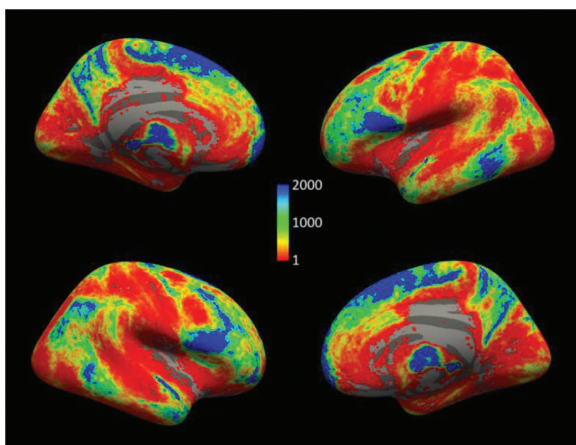
New techniques demonstrate coverage of the cortical surface by the terminations of manually labeled tractography streamlines. Image: Maffei et al. Figure 6 from www.ncbi.nlm.nih.gov/pmc/articles/PMC8835483/

Using diffusion MRI data acquired with ultra-high gradient strength to improve tractography in routine-quality data.

Maffei C, Lee C, Planich M, Ramprasad M, Ravi N, Trainor D, Urban Z, Kim M, Jones RJ, Henin A, Hofmann SG, Pizzagalli DA, Auerbach RP, **Gabrieli JDE**, **Whitfield-Gabrieli S**, Greve DN, Haber SN, Yendiki A. | *Neuroimage* (Dec 2021)

The development of scanners with ultrahigh gradient strength has led to dramatic improvements in the spatial, angular, and diffusion resolution feasible with in vivo diffusion MRI. In this study, Gabrieli, Whitfield-Gabrieli, and colleagues updated classical protocols to adapt them to greater volume and variability that can be produced from today's state-of-the-art diffusion MRI data. The outcomes of this work include both a new, comprehensive atlas of white-matter pathways and an updated version of a tractography toolbox.

Epitope-preserving magnified analysis of proteome (eMAP).

Park J, Khan S, Yun DH, Ku T, Villa KL, Lee JE, Zhang Q, Park J, **Feng G**, Nedivi E, Chung K. | *Sci Adv* (Nov 2021)

Synthetic tissue-hydrogel methods have enabled super-resolution investigation of biological systems using diffraction-limited microscopy. However, chemical modification by fixatives can cause loss of antigenicity, limiting molecular interrogation of the tissue gel. In this advance, scientists pioneered epitope-preserving magnified analysis of proteome (eMAP) that uses purely physical tissue-gel hybridization to minimize the loss of antigenicity while allowing permanent anchoring of biomolecules.

Comparative cellular analysis of motor cortex in human, marmoset and mouse.

Bakken TE, Jorstad NL, et al. | *Nature* (Oct 2021)

The primary motor cortex is essential for voluntary fine-motor control and is functionally conserved across mammals. Using high-throughput transcriptomic and epigenomic profiling of more than 450,000 single nuclei in humans, marmosets, and mice, global collaborators including Guoping Feng demonstrated a broadly conserved cellular makeup of this region, with similarities that mirror evolutionary distance and are consistent between the transcriptome and epigenome.

The widespread IS200/IS605 transposon family encodes diverse programmable RNA-guided endonucleases.

Altae-Tran H, Kannan S, Demircioglu FE, Oshiro R, Nety SP, McKay LJ, Dlakić M, Inskeep WP, Makarova KS, Macrae RK, Koonin EV, **Zhang F**. | *Science* (Oct 2021)

IscB proteins are likely ancestors of the RNA-guided endonuclease Cas9, but the functions of IscB and its interactions with RNA remain uncharacterized. Using evolutionary analysis, RNA sequencing, and biochemical experiments, the Zhang team reconstructed the evolution of CRISPR-Cas9 systems from IS200/IS605 transposons, revealing their strong potential for biotechnology development.
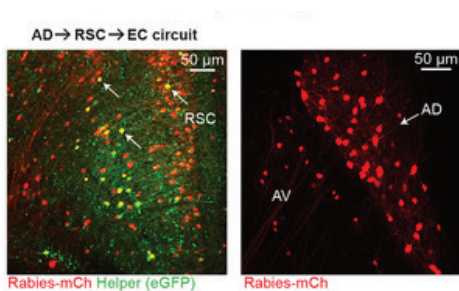
Viral tracing shows anterodorsal and anteroventral inputs to entorhinal cortex-projecting neurons in the retrosplenial cortex. Image: Roy et al. Figure 4 from www.ncbi.nlm.nih.gov/pmc/articles/PMC8376805/

Anterior thalamic dysfunction underlies cognitive deficits in a subset of neuropsychiatric disease models.

Roy DS, Zhang Y, Aida T, Choi S, Chen Q, Hou Y, Lea NE, Skaggs KM, Quay JC, Liew M, Maisano H, Le V, Jones C, Xu J, Kong D, Sullivan HA, Saunders A, McCarroll SA, Wickersham IR, **Feng G**. | *Neuron* (Aug 2021)

In this study, a team of researchers led by Guoping Feng found that many autism and schizophrenia risk genes are expressed in the anterodorsal subdivision of anterior thalamic nuclei, which has reciprocal connectivity with learning and memory structures. The findings identify converging cellular-to-circuit mechanisms underlying cognitive deficits in a subset of neuropsychiatric disease models.

Compact RNA editors with small Cas13 proteins.

Kannan S, Altae-Tran H, Jin X, Madigan VJ, Oshiro R, Makarova KS, Koonin EV, **Zhang F**. | *Nat Biotechnol* (Aug 2021)

CRISPR-Cas13 systems have been developed for precise RNA editing and can potentially be used therapeutically when temporary changes are desirable. Zhang lab researchers identified and characterized an ultrasmall family of Cas13b proteins, which appear to be useful in overcoming the limitations of widely used vectors for gene delivery.

Efficient embryonic homozygous gene conversion via RAD51-enhanced interhomolog repair.

Wilde JJ, Aida T, Del Rosario RCH, Kaiser T, Qi P, Wienisch M, Zhang Q, Colvin S, **Feng G**. | *Cell* (Jun 2021)

Searching for factors to improve efficiency for therapeutic applications, biotechnology, and generation of non-human primate models of disease, researchers found that the strand exchange protein RAD51 can significantly increase Cas9-mediated homozygous knockin in mouse embryos through an interhomolog repair mechanism. The findings describe an efficient method for enhanced gene conversion.

Functional alterations in cerebellar functional connectivity in anxiety disorders.

Lee YJ, Guell X, Hubbard NA, Siless V, Frosch IR, Goncalves M, Lo N, Nair A, Ghosh SS, Hofmann SG, Auerbach RP, Pizzagalli DA, Yendiki A, **Gabrieli JDE**, **Whitfield-Gabrieli S**, Anteraper SA. | *Cerebellum* (Jun 2021)

Adolescents with anxiety disorders exhibit excessive emotional and somatic arousal, and neuroimaging studies of their brains have shown abnormal cerebral cortical activation and connectivity. In this study, researchers demonstrated that adolescents with an anxiety disorder show significant hyperconnectivity between salience-motor dentate nuclei functional territory and cerebral cortical salience-motor regions compared to controls. This observation highlights the relevance of dentate nuclei as a potential clinical and subclinical marker of anxiety.

In the Zhang lab, graduate student Han Altae-Tran engineered two newly discovered classes of DNA-cutting proteins. Photo: Steph Stevens
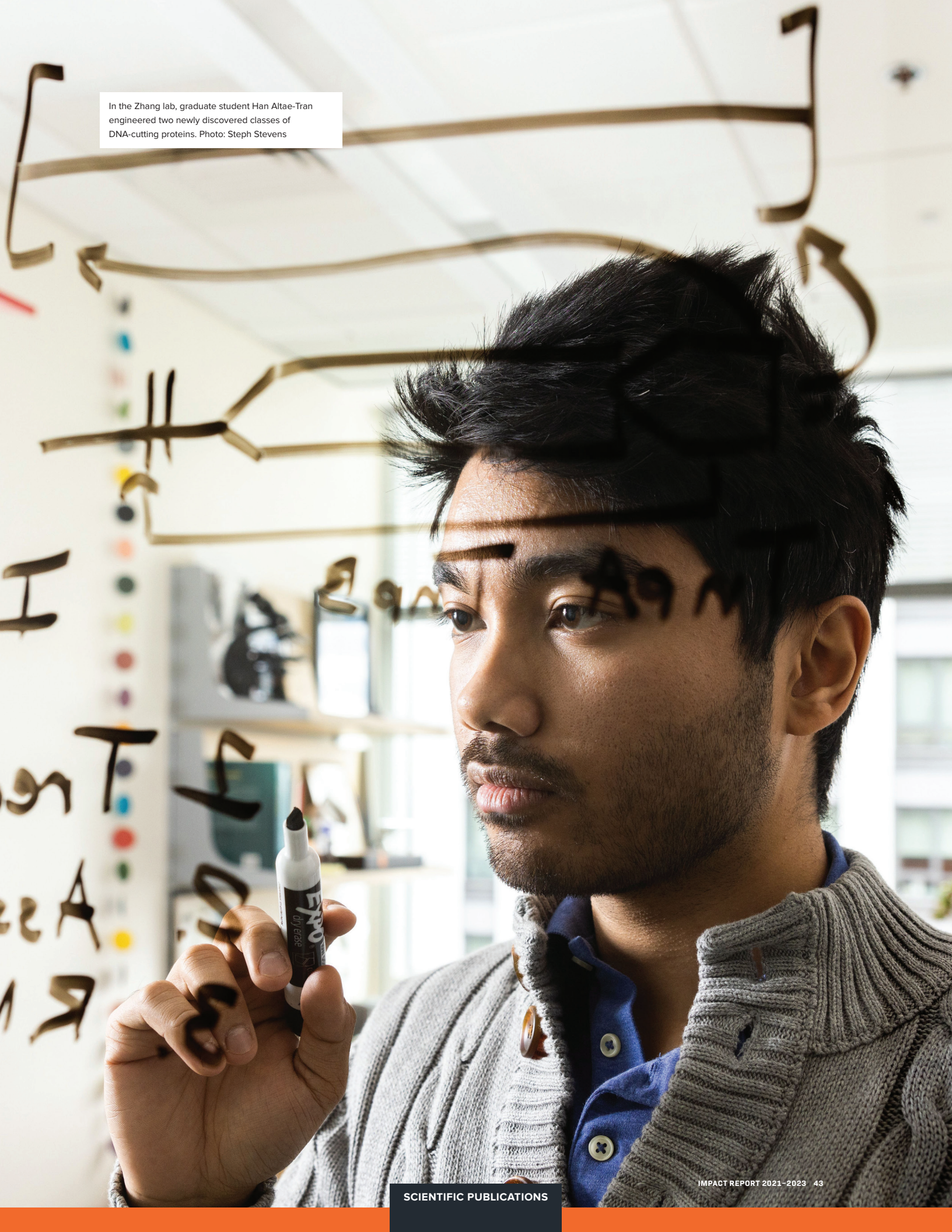
FUTURE DIRECTIONS

Each new discovery opens a door to the next one as Poitras Center researchers pursue bold approaches to predicting and treating major mental illness.

Moving closer and closer to the clinic

In their own words

"We are really excited about the translational possibilities of our basic research — advances we could not have made without the vision of the Poitras family and their remarkable support."

So says Guoping Feng, summing up the sentiment of his colleagues at the Poitras Center.

In the paragraphs that follow, these dedicated scientists describe some of the exciting directions their research will be taking in the near future. Their continuing generation of new pathways to improve human mental health underscores, once again, the vital importance of the Poitras Center for Psychiatric Disorders Research for society at large.

John Gabrieli and Susan Whitfield-Gabrieli

Empowering patients through personalized, self-guided interventions

"We seek to leverage the power of real-time fMRI neurofeedback to fine-tune highly individualized behavioral therapies and rebalance the patterns of aberrant brain network activity that underlie a broad range of mental disorders, from bipolar disorder to anxiety and major depression. Our vision is to create a technology-based training platform that supports individuals living with mental illness, ultimately enabling them to recognize the onset of negative mental states in real time in their daily lives, initiate behavioral interventions targeted to their own precise neural architecture and activity patterns, and create brain network dynamics that are conducive to positive mental health. The training platform will help patients reach their full potential in the context of their lives, communities, and societies."

Feng Zhang

Overcoming limitations in delivering therapeutics

"For next steps, we are using the tools and approaches we have established to develop additional cellular models of neuropsychiatric diseases. Currently, a key obstacle in treating these diseases is the safe and effective delivery of therapies into the brain. We are working to develop both virus-based and non-virus-based novel delivery systems that could efficiently pass the blood-brain barrier. We are also in the process of engineering several of the new DNA-modifying tools that we have found in nature to test them in mouse models of disease. These new systems, from genetic elements called retrotransposons to extracellular contractile injection systems, hold the promise of overcoming many of the limitations of today's modalities, including small cargo size and eliciting an immune response."

Guoping Feng

Identifying dysfunctional cells in psychiatric disorders as targets for therapeutics

"For the first time in the history of schizophrenia research, large-scale human genomic studies have identified genetic mutations that dramatically increase the risk for schizophrenia. We now have new animal models that contain these pathogenic mutations found in human patients. These new models allow us to study how these mutations change brain development and function, and how these changes may contribute to schizophrenia pathology. As described in the report, we are starting to reveal some of the neurobiological mechanisms relevant to schizophrenia at cellular and circuit levels. Our next goal is to use single-cell transcriptomic technology to identify particular brain cell types most affected by these mutations and identify specific molecular targets for developing effective therapeutics."

Poitras Center *for*
Psychiatric Disorders Research

McGovern Institute for Brain Research at MIT
77 Massachusetts Avenue 46-3160
Cambridge, MA 02139

mcgovern.mit.edu/poitras

617.324.0134

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