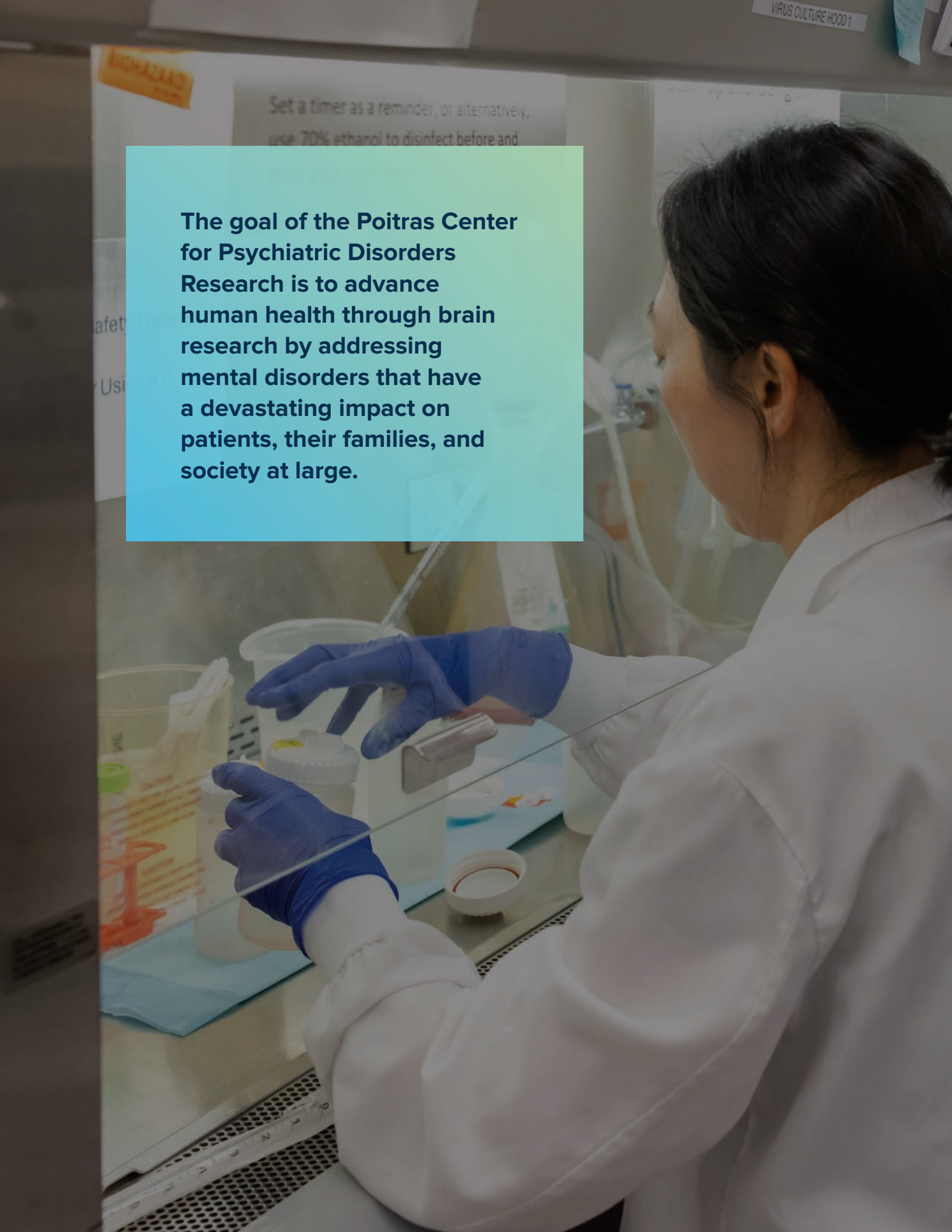
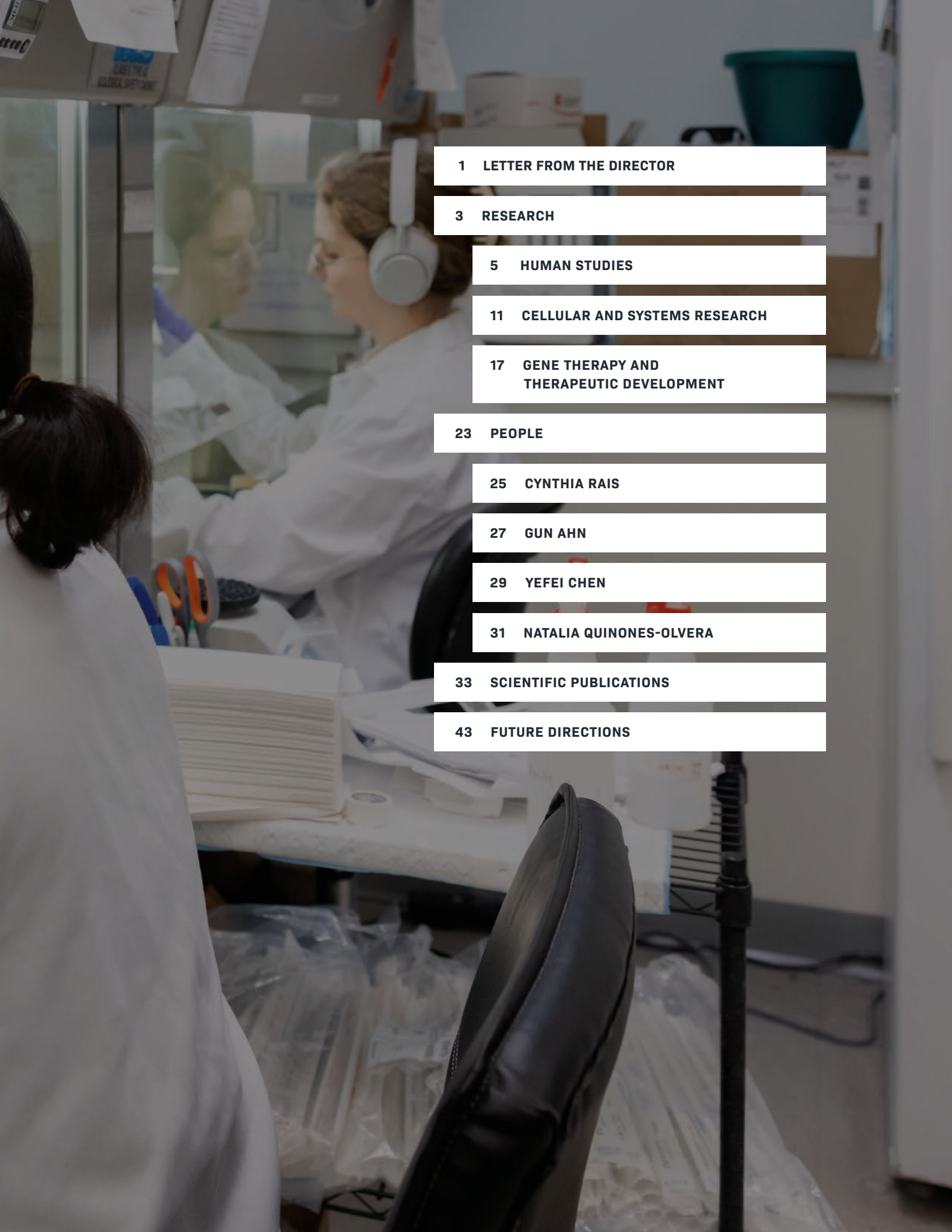
POITRAS CENTER FOR PSYCHIATRIC DISORDERS RESEARCH

IMPACT REPORT

2023–2025



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

Severe mental illnesses remain pernicious threats to human health and well-being, but thanks to continued progress made in the Poitras Center for Psychiatric Disorders Research, we are improving prevention, diagnostic, and treatment strategies.

Poitras Center scientists are undertaking innovative studies on psychiatric diseases and disorders to reveal new and promising paths toward treating them. Our researchers are at the forefront of the field, decoding the genetic, neurobiological, and circuit-level basis of these complex conditions. Poitras Center support helped hone the first U.S. Food and Drug Administration-approved CRISPR gene therapy in 2023—an auspicious milestone that has revolutionized the treatment landscape and laid an important foundation for future gene therapies.

Over the 18 years since its inception, the Poitras Center has enriched our knowledge of psychiatric illnesses including schizophrenia, major depression, anxiety, bipolar disorder, and obsessive-compulsive disorder. The Center has enabled us to reach our fullest understanding to date of these devastating conditions.

Our recent progress, detailed in this report, is owed to the vision and generosity of the Poitras family. We are deeply grateful for their renewed commitment this past year, as their support will continue to catalyze and propel crucial projects that are redefining how we study, understand, and treat major mental illnesses.

A VIGNETTE OF OUR RECENT ADVANCES

The lab of Feng Zhang continues to create novel molecular tools that target the origin of genetic diseases. Their newest technologies are Tandem Interspaced Guide RNA (TIGR) systems that are more flexible and precise than current genome engineering methods—exceeding some capabilities of CRISPR-Cas9-based systems. They've also modified a bacterial RNA-guided enzyme to edit human DNA and designed new CRISPR enzymes that can stealthily evade the immune system to drastically improve the safety of gene therapies. By curating a versatile toolkit, the Zhang lab now has a suite of genome-editing platforms that could remedy a spectrum of disease-causing dysfunctions, including those affecting the brain.

Guoping Feng's team has made strides in their ambitious search for the neural circuitry driving major mental illnesses, and their studies have unearthed pivotal findings. Recently, the team lent new clarity to the genetic basis of schizophrenia and uncovered a neural pathway strongly linked to severe depression—important steps toward finally answering questions that have perplexed scientists for decades. Primate research is accelerating the pace of their work, allowing the Feng team to gain a firm understanding of the neurobiology driving psychiatric conditions to learn exactly how they arise and how they might be treated in humans.

By applying cutting-edge neuroimaging and machine learning tools, teams led by John Gabrieli and Susan Whitfield-Gabrieli are probing major mental health disorders in adult and adolescent patients. Their research is laying the groundwork for strategies that can predict which patients may or may not benefit from a given treatment for more personalized care. Moreover, they are exploring

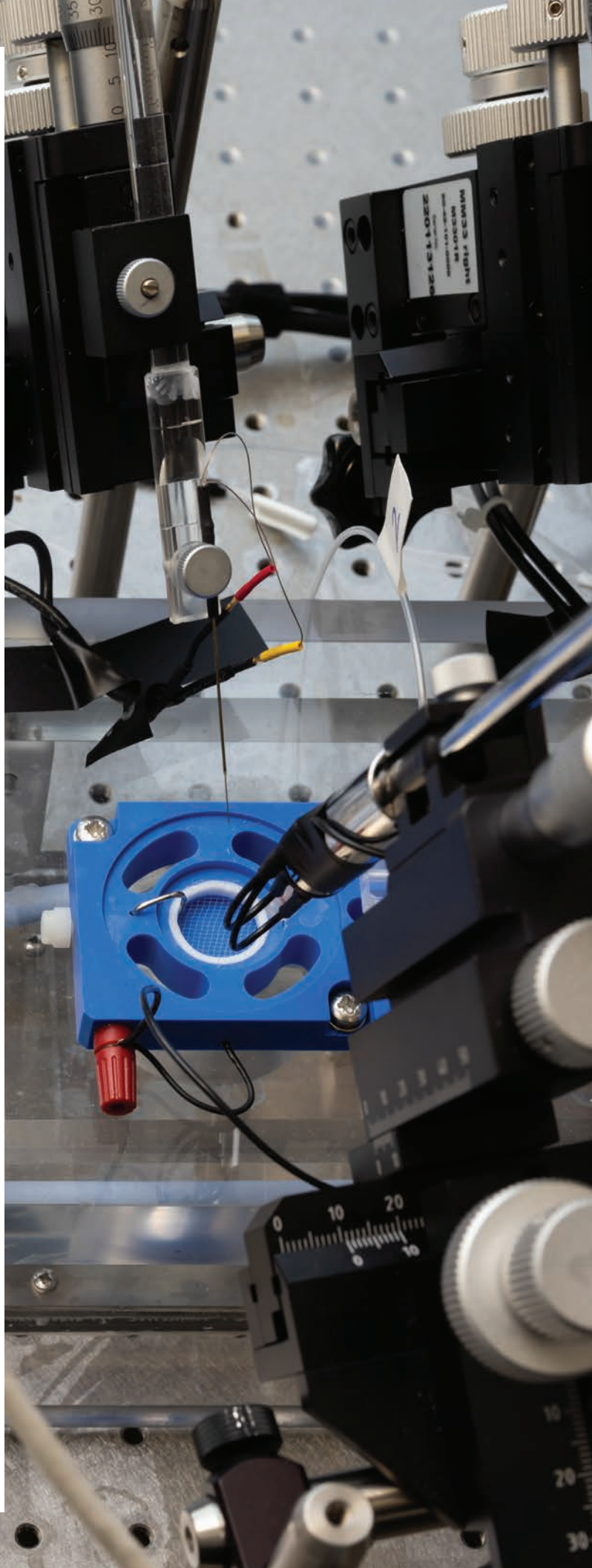
how neurofeedback — a promising method for treating brain conditions such as schizophrenia — could be optimized for maximum benefits. They have also discovered the brain connections that may foster psychosis symptoms, often an early sign of schizophrenia, and could provide biomarkers that can be exploited for precise therapeutic strategies.

We now intend to build on our strong progress by expanding the Poitras Center to new investigators and approaches for studying major mental illness. A team led by Nancy Kanwisher and Evelina Fedorenko will work to uncover how differences in internal speech and reasoning in schizophrenia may drive the disease's cognitive symptoms. In another project, Mark Harnett and Poitras Fellow Cynthia Rais aim to explore how clinical doses of ketamine can alter brain circuits, particularly in the context of treatment-resistant depression. Jim DiCarlo's lab is investigating new ways to treat mood disorders via visual interventions that could alter emotion processing and unlock drug-free and non-invasive approaches. These new projects are bolstering the cadre of leading investigators in the Poitras Center while also extending the Center's reach and its foreseeable impact on society.

We greatly appreciate the Poitras family's longtime support in seeding our daring projects. Such high-risk yet high-reward studies are often the gateway to reaching the most impactful discoveries, and we are honored to help realize their bold vision for psychiatric disorders research.

Most importantly, though, the Poitras family's commitment is brightening the future for the many patients and families living with major mental illnesses. We cannot thank the family enough for their invaluable partnership.

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 using machine learning to enhance social anxiety treatments, leveraging real-time neurofeedback to treat schizophrenia, uncovering the brain circuitry of depression, devising novel genome-editing methods, and creating CRISPR enzymes that dodge the immune system.

Human Studies

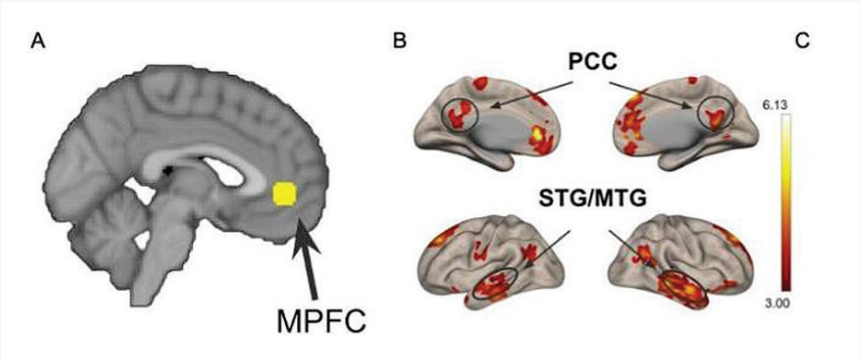
Part of the vanguard in neuroimaging research, John Gabrieli and Susan Whitfield-Gabrieli are capturing important links between brain activity and health outcomes in psychiatric disorders to unlock novel ways to treat them.

Linking psychosis-risk symptoms to brain connectivity

Neuroscientists have discovered that people with schizophrenia show atypical signaling patterns in the brain. These include hyperconnectivity of the default mode network (DMN), which turns on when we have internal thoughts, such as when we reminisce on the past or contemplate our feelings. "If connections within the DMN are too strong, this can lead to rumination and other persistent negative thinking," says Susan Whitfield-Gabrieli, the Tommy Fuss Endowed Professor of Precision Psychiatry at Massachusetts General Hospital and a McGovern Institute research affiliate.

She and her team have been partnering with researchers at the McGovern Institute to probe the role of the DMN in severe brain conditions. They suspect that overactive functional connectivity of the DMN circuit might be present in the brains of people with a high risk for psychosis, which can be an early sign of schizophrenia. "We know that people with greater DMN connectivity experience harsher symptoms of psychosis. But we are still unsure of the extent of this hyperconnectivity and how exactly this is tethered to mental health symptoms," Whitfield-Gabrieli explains.

The researchers set out to investigate these unresolved questions. Through an international collaboration, they recruited 93 healthy controls and 158 high-risk psychosis patients seeking care at the Shanghai Mental Health Center in China. Participants took clinical and cognitive assessments and also underwent functional magnetic resonance imaging (fMRI) to monitor their brain connectivity. "Indeed, compared to controls, we found that psychosis-risk patients had greater functional



In people with a high risk for psychosis, Whitfield-Gabrieli's team uncovered that greater connectivity between the medial prefrontal cortex (MPFC) and two other brain areas—the posterior cingulate cortex (PCC) and superior and middle temporal gyri (STG/MTG)—was linked to different mental health symptoms. Image: Whitfield-Gabrieli lab

connectivity within the DMN," notes Whitfield-Gabrieli. "We also uncovered a surprising observation."

At the core of the default mode network lies the medial prefrontal cortex—a crucial brain region that processes memories, facilitates introspection, and decodes social information. It receives signals gathered by the posterior cingulate cortex, another region in the DMN that fosters internal thoughts and memory recall. "The signaling stream between these two regions was significantly correlated with anxiety," says Whitfield-Gabrieli.

She also notes that the pathway between the medial prefrontal cortex and the superior and middle temporal gyri—auditory cortices—was linked to low motivation and trouble with daily tasks, among other negative symptoms. "As far as we know, this research is the first to link hyperconnectivity between the DMN and these auditory cortices to negative symptoms in people at risk for psychosis," says Whitfield-Gabrieli.

"If we follow these clues to more deeply explore how the DMN is affected in psychosis and other brain conditions, we could develop strategies that target these areas to improve mental health outcomes for patients, and even help prevent the full expression of schizophrenia in those with a high risk for the disease," she adds.

Using machine learning to enhance social anxiety treatments

Social anxiety disorder can deprive patients of strong relationships and human connection, leaving individuals feeling isolated and alone. Cognitive behavioral therapy (CBT) is often used to help people manage their social anxiety. But only half of patients actually benefit from this treatment method.

"There are high rates of initial treatment failures in psychiatric disorders, like social anxiety, that prolong patient suffering, as physicians must try one treatment after another. It would be valuable if there were a scientific approach to selecting an initial treatment that is more likely to immediately help a patient," says John Gabrieli, the Grover Hermann Professor of Health Sciences and Technology and Brain and Cognitive Science at MIT.

Susan Whitfield-Gabrieli is leveraging brain imaging studies to find new interventions for psychiatric disorders. Photo: Caitlin Cunningham

Researchers in the lab of John Gabrieli are devising methods to predict treatment outcomes for severe mental illnesses. Photo: Steph Stevens

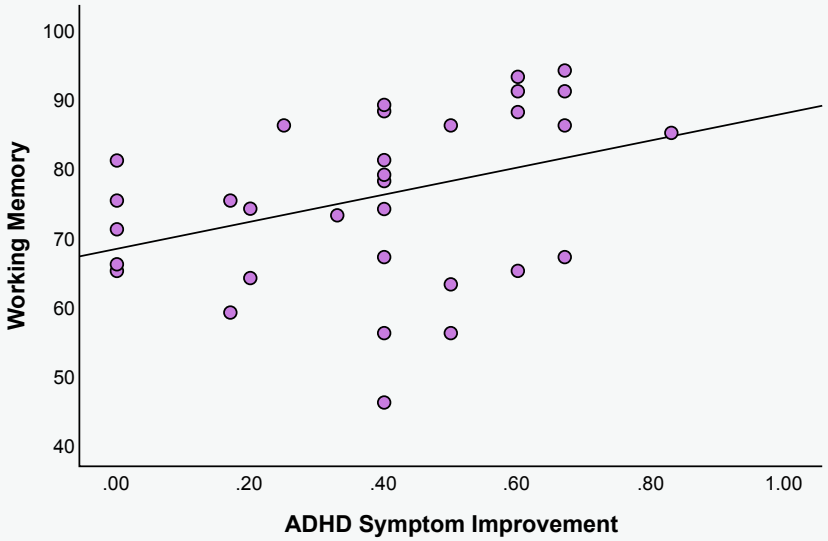
John Gabrieli and his team are at the forefront of the field of precision psychiatry. They are developing data-driven methods that use biomarkers and other measures to predict which patients will benefit from a specific treatment, such as CBT. This could transform care for people with social anxiety as well as a broad spectrum of conditions. "Knowing which people will benefit from a particular therapy can help patients pursue the option best-suited to their unique condition," says Gabrieli. "Importantly, these tools are low-cost and relatively easy to implement, ensuring that many could reap the benefits of this work."

In a study published in *PLOS One* in March 2025, Gabrieli and colleagues analyzed data from 157 patients with social anxiety who underwent CBT. The researchers compiled patient information — including psychiatric history, demographics, and clinical questionnaires. They fed the data into several different machine-learning models to pinpoint which features were most important for prediction. In analyzing their results, the team found that all models performed similarly and could accurately predict which patients would or would not benefit from the CBT treatment.

"We gleaned some additional insights," Gabrieli reports. "First, we discovered that more severe social anxiety symptoms prior to CBT led to a better response to the therapy." He says that this is notable because this challenges a belief in the field that worse symptoms are associated with a more limited response to CBT.

"Our study also pointed to the Liebowitz Social Anxiety Scale — a common clinical assessment used to gauge social anxiety severity — as the most informative measure in achieving precise predictions," notes Gabrieli. He says that, because the scale captures symptom severity, this could explain its importance in predicting treatment outcomes.

Encouraged by their progress so far, the Gabrieli team hopes their work will inform personalized treatment plans that can significantly improve clinical care for patients with social anxiety disorder and other mental health challenges.



The Gabrieli lab found that working memory abilities were significantly correlated with improved symptoms in adults taking stimulants to treat attention-deficit/hyperactivity disorder (ADHD). Image: Gabrieli lab

Predicting the effectiveness of stimulants for ADHD

Stimulants are often the first-line treatment for attention-deficit/hyperactivity disorder (ADHD) because they can subdue symptoms and improve focus. But stimulants are only effective in about 60 percent of adult patients—far weaker than in children and teens. "For people with ADHD who begin taking stimulants in adulthood, research suggests that nearly 42 percent of them change their medication due to side effects," says John Gabrieli. He and his lab are investigating new ways to improve therapeutic strategies for adults with ADHD and find a more effective alternative to the current trial-and-error approach.

Diffusion tensor imaging (DTI) may be the key to forming new predictive strategies. It's an MRI-based method (also called dMRI) that tracks the movement of water

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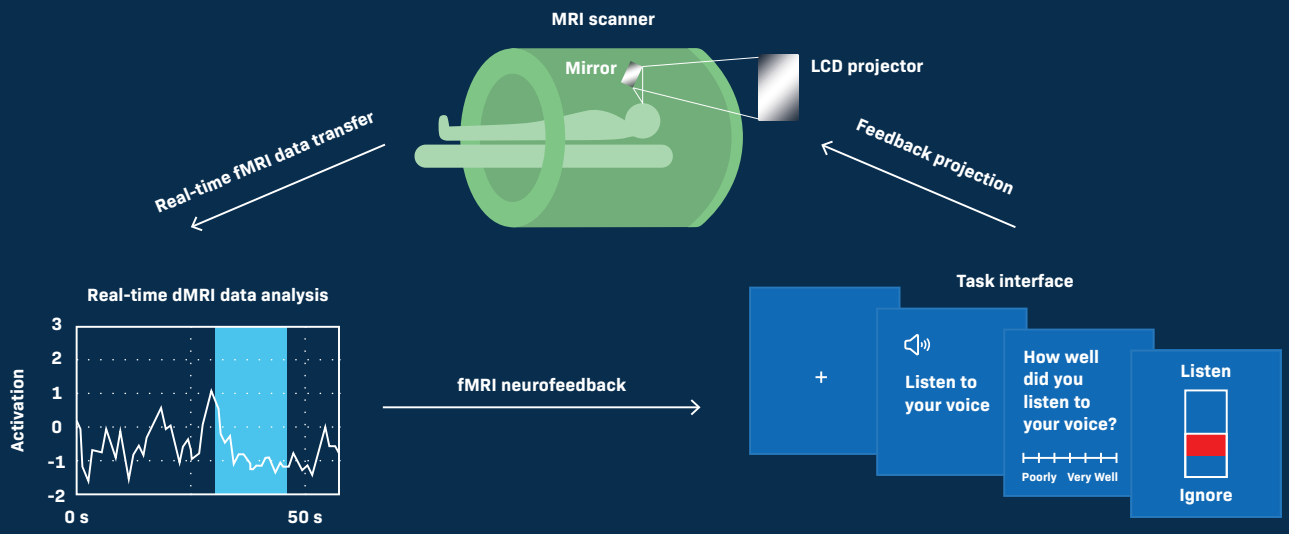

A research team led by Susan Whitfield-Gabrieli and John Gabrieli is exploring how real-time neurofeedback via fMRI could be effectively used to treat auditory hallucinations. Image: Gabrieli lab

in the brain via magnetic fields, enabling researchers to map the elaborate white matter "highways" that link various brain regions. "DTI helps us see how different parts of the brain are communicating," Gabrieli explains.

In their pilot study—published in the *Journal of Attention Disorders* in March 2024—the Gabrieli team recruited a cohort of 36 adult patients not yet taking ADHD medication. Participants underwent DTI, completed cognitive assessments, and were then prescribed either one of two common stimulants at random. They completed additional cognitive assessments seven and 17 weeks later.

The team found that patients who responded better to a given stimulant had greater white-matter connectivity in the striatum, a region that facilitates learning and reward processing. Better working memory, however, was linked to favorable treatment outcomes across all patients. "Those with sharper working memory might have higher executive functioning overall, which we know can lead to improved symptoms when taking stimulants. Our research strengthens the case that executive functions might be a reliable predictor of how well stimulants will manage a person's ADHD," says Gabrieli.

Leveraging real-time neurofeedback to treat schizophrenia

Some people diagnosed with schizophrenia experience auditory hallucinations that cause extreme confusion and distress. Because these hallucinations are often treatment resistant, new strategies that can mitigate these symptoms are desperately needed.

Susan Whitfield-Gabrieli's team, in collaboration with the lab of John Gabrieli, is decrypting the brain circuits driving auditory hallucinations to develop better therapeutic approaches. As pioneers in the neuroimaging field, the researchers are investigating how functional magnetic resonance imaging (fMRI) neurofeedback could be used to treat these symptoms.

Neurofeedback—monitoring brain activity in real time—is a flexible tool that can be used to track the progression or decline of auditory hallucinations. "Since these symptoms are linked to changes in the brain, this technique can provide real-time feedback and help patients gauge their progress by tracking shifts in brain function," Whitfield-Gabrieli explains.

She and her team monitored the brain activity of adults with schizoaffective disorders and frequent medication-resistant auditory hallucinations during neurofeedback sessions via fMRI. Patients were instructed to increase their brain activity when they heard their own voice and decrease activity when they heard the voice of another person.

Each patient was randomly assigned to receive neurofeedback of the auditory cortex in the superior temporal gyrus — a hub for speech and language processing that is thinner in patients with these hallucinations — or their motor cortex for three sessions. All patients were trained in mindfulness practices and were told to exercise these skills during neurofeedback sessions.

The researchers' intervention unearthed breakthrough discoveries. "We found that, at baseline, people with more severe auditory hallucinations had greater connectivity between the medial prefrontal cortex and posterior cingulate cortex — two regions within the default mode network," notes Whitfield-Gabrieli. "But a particularly new and important finding emerged." She reports that patients who received neurofeedback of their auditory cortices were able to reduce the activity between this region and the default mode network.

This fascinating study points to specific brain connections of interest during fMRI neurofeedback — offering a more targeted approach to treating auditory hallucinations in schizophrenia.

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The effect of lifetime stressors on adolescent brain health

During adolescence, the brain's connections begin to take a more permanent shape. It's a critical — and vulnerable — time for brain development. Young people who experience major life stressors, such as the death of a loved one or physical abuse, are more likely to experience anxiety and depression over their lifetime. "We know that teens with anxiety and depression have atypical signaling in the brain. But we have yet to investigate the relationship between life stressors and neurobiology over time," says Susan Whitfield-Gabrieli.

In a recent study, Whitfield-Gabrieli and colleagues at the McGovern Institute assembled a cohort of 107 adolescents from the Boston area who had been diagnosed with anxiety and depressive disorders. They gathered information regarding the patients' symptoms and key life stressors, such as interpersonal loss, humiliation, and physical danger. The researchers then observed patients' brain circuitry while at rest via fMRI. Patients completed clinical assessments again at six and 12 months.

"We discovered that entrapment — feeling stuck in an adverse and uncontrollable circumstance with no escape — was the greatest indicator of depression and anxiety," says Whitfield-Gabrieli. She explains that getting bullied, walking regularly through a threatening neighborhood to go to school, or having a verbally abusive parent can give rise to feelings of entrapment.

"Entrapment was also linked to anxiety symptoms in adolescents with greater connectivity of the default mode network," she says. Interestingly, stronger connectivity between the frontoparietal region and the default mode network appeared to be associated with depression.

According to Whitfield-Gabrieli, this important study is the first to bring to light how major life stressors influence mental health among young people, and points to more precise indications of how exactly these stressors mold the developing brain.

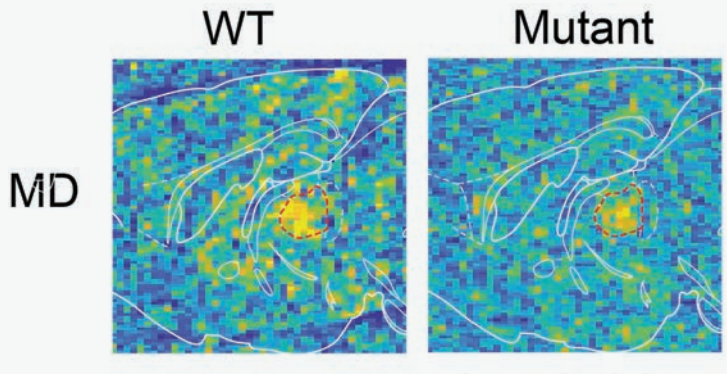
Cellular and Systems Research

The lab of Guoping Feng is deploying crucial studies to discover how and why brain systems become impaired in psychiatric illnesses—foundational to creating new therapeutic approaches that can repair dysfunctional neural circuits.

Deciphering cognitive deficits in schizophrenia

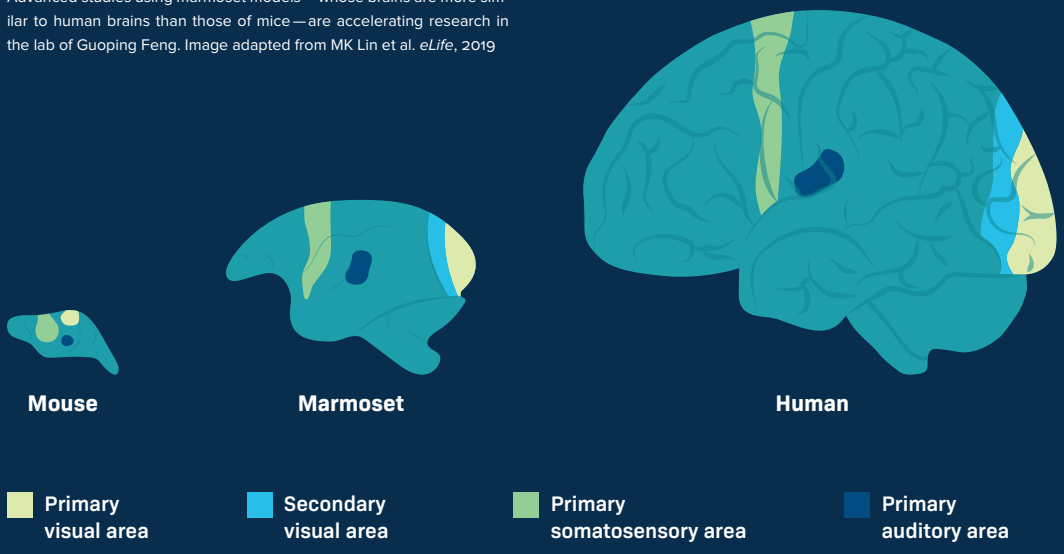
Part of the human mind's immense power is its ability to update beliefs when presented with new information. In schizophrenia, there may be neurobiological differences that make it difficult for patients to revise their beliefs, and impairments in this process could trigger psychosis. The mechanisms underlying belief adjustment in schizophrenia have evaded scientists' grasp for years. Guoping Feng, the James W. (1963) and Patricia T. Poitras Professor of Neuroscience, and postdoctoral researcher Tingting Zhou are making bold moves in their search for them.

"A major problem in schizophrenia research is that scientists have long lacked appropriate animal models for the disorder. And even with the best ones available, linking the animals' behaviors to the correct neurobiological cause has been difficult," says Feng. He is working with Zhou and colleagues to overcome this barrier by developing mouse models that closely resemble some aspects of schizophrenia. These mice carry a mutation in *GRIN2A*, which encodes a protein that is critical to



Feng's team found that the mediodorsal thalamus (circled in red) shows reduced activity in mutant *GRIN2A* mice compared to wild-type mice, suggesting that it may drive certain cognitive impairments in schizophrenia. Image: Feng lab

Advanced studies using marmoset models—whose brains are more similar to human brains than those of mice—are accelerating research in the lab of Guoping Feng. Image adapted from MK Lin et al. *eLife*, 2019



PRIMATE MODELS: ACCELERATING THE LAB-TO-CLINIC PIPELINE

Testing therapeutic candidates in primate models can be an important step in the drug development pipeline. Such research allows scientists to better position nascent treatments and technologies for clinical trials. Marmoset studies, in particular, are rapidly advancing the state of scientific inquiry. Humans' evolutionary cousin, these small primates behave similarly to us in social contexts and cognitive tasks, and they have comparable brain structures.

Researchers in the Poitras Center are conducting critical marmoset research to make unprecedented findings in neuroscience—from mining new wisdom of cognitive processes and how they become impaired in psychiatric conditions to pinpointing the genetic basis of brain diseases and disorders.

The lab of Guoping Feng has drastically improved marmoset models of neurodevelopmental disorders to decode these conditions and hone potential therapies. His team has manipulated marmoset embryos by deploying major CRISPR technologies to create models for Rett syndrome—a neurological disorder that causes severe deficits in motor and language skills—and those containing mutations in the *SHANK3* gene, which can underlie severe autism. These advanced primate models are allowing the Feng lab to test novel strategies that mitigate behavioral and circuit deficits in neurodevelopmental disorders, helping propel their research towards long-awaited cures.

In a landmark achievement, the Feng lab generated a comprehensive database of the entire marmoset brain at the single-cell and single-nucleus level. The researchers are compiling an extensive map—spanning over 2 million brain cells—that scientists can use to more quickly detangle complex brain conditions and reveal precise therapeutic targets.

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>
> **–GUOPING FENG**

brain plasticity. Scientists have found that certain mutations in this gene confer a high risk for schizophrenia. However, the downstream consequences of this genetic instigator — especially its effects on behavior — are still poorly understood.

Aiming to fill this gap, the Feng team coupled their genetic model with a foraging task designed to encourage belief updating in mice. The scientists also leveraged computational tools to precisely track the animals' behaviors during the task. In their experiments, the researchers found that *GRIN2A* mutant mice showed unstable behaviors and were slower to update their beliefs compared to wild-type mice.

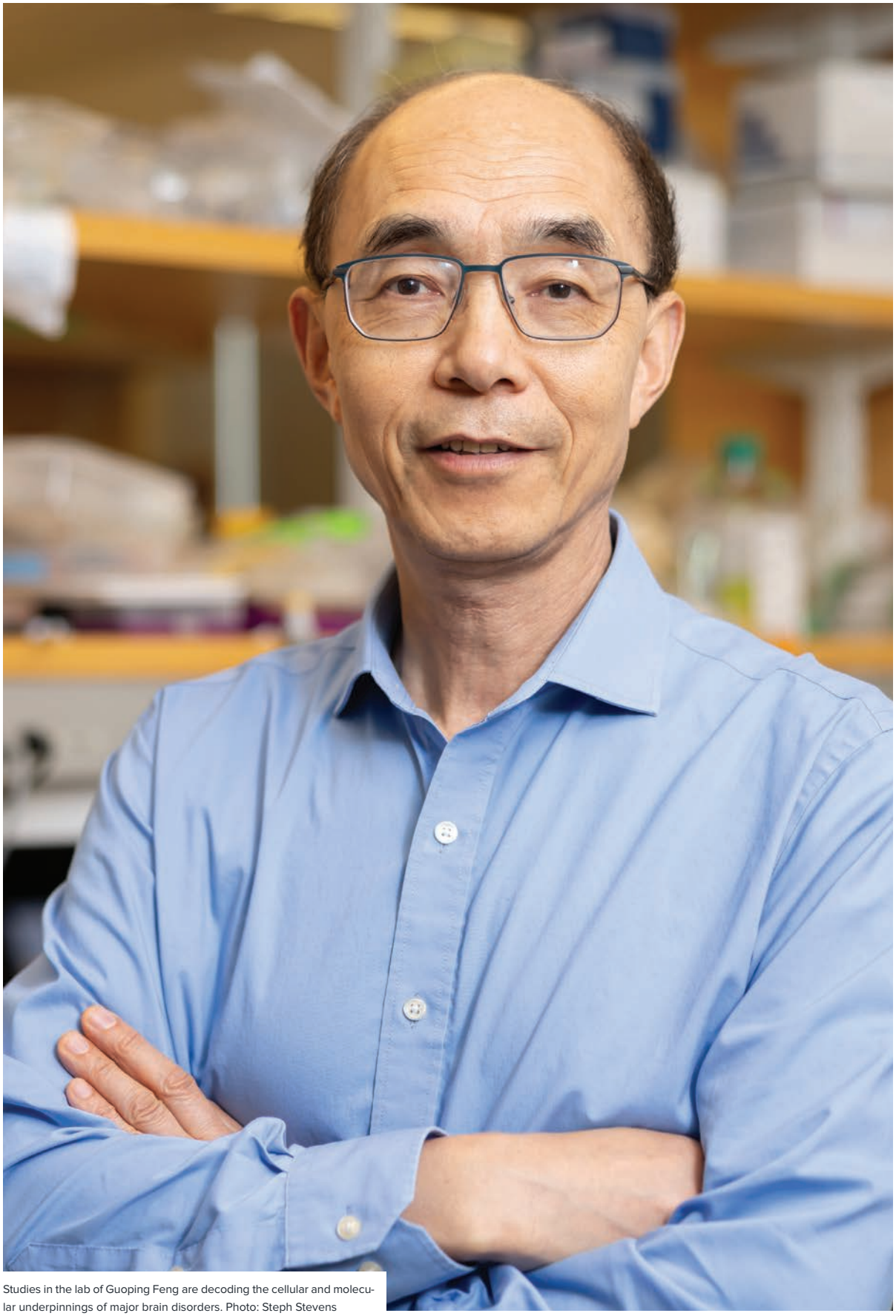
The Feng team also applied functional ultrasound imaging and electrophysiological recording to monitor the mice's brain activity. "The mediodorsal thalamus is heavily involved in higher-level cognitive tasks and has been found to be dysfunctional in schizophrenia patients. In *GRIN2A* mutant mice, this region appeared to be under-functioning," says Feng. When the researchers inhibited mediodorsal thalamus neurons in wild-type mice using optogenetics, they observed behaviors similar to those of the mutant mice. On the other hand, when the team enhanced the activity of these same neurons in the mutant mice, this reduced deficits in the behavioral task.

According to this cutting-edge research, the mediodorsal thalamus is a likely suspect in driving some cognitive dysfunctions in schizophrenia. Now, Feng, Zhou and colleagues are poised to further delineate the role of the mediodorsal thalamus in the disease and make inroads into next-generation therapies that target it.

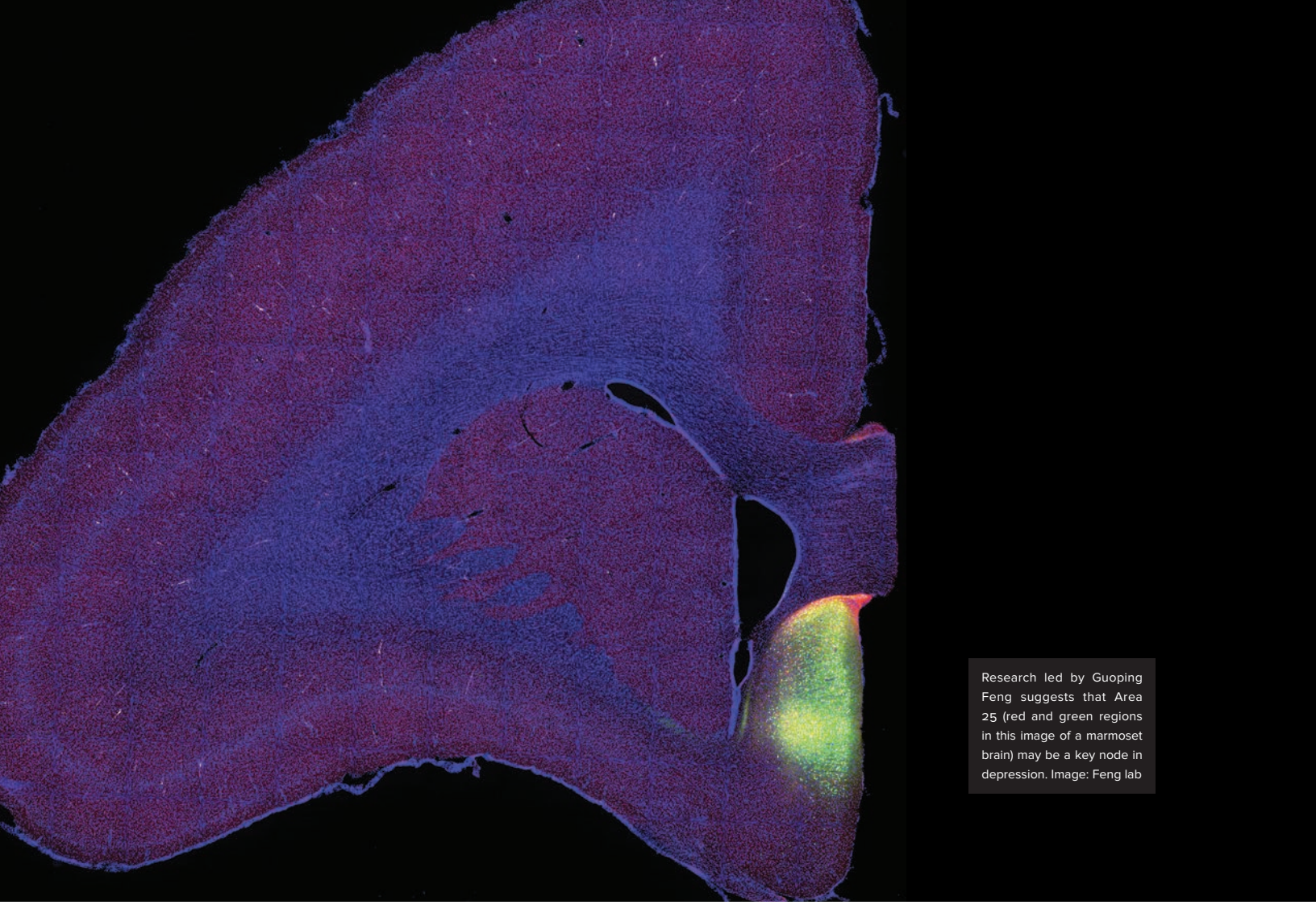
Uncovering the brain circuitry of depression

Depression is a widespread mental health challenge affecting over 280 million people worldwide. Many of us know someone in its clutches. The neural machinery driving depression is unclear, even with years of research and extensive brain mapping in rodent models. "Nonhuman primates share more similar biology and brain structure to humans," says Feng. "They are a better model for capturing the unique brain circuitry in depression and understanding how this complicated disorder manifests in humans."

Wedged in the middle of the frontal lobe is a small region called Area 25. Area 25 exists in both humans and primates, and it is known to help regulate mood. It has emerged as a key location of interest in the Feng lab's depression studies. Clinical research has found Area 25 to be overactive in human patients with depression.



Studies in the lab of Guoping Feng are decoding the cellular and molecular underpinnings of major brain disorders. Photo: Steph Stevens



Research led by Guoping Feng suggests that Area 25 (red and green regions in this image of a marmoset brain) may be a key node in depression. Image: Feng lab

Some studies have found that using deep brain stimulation to calm down this area via high-frequency electrical pulses can curb the severity of patients' symptoms for prolonged periods. Interestingly, when Area 25 is activated in primate brains, this overstimulation arouses depression-like symptoms in the animals.

With ample evidence pointing to Area 25 as a vital node in depression, Feng and colleagues set out to probe the brain regions that interact with Area 25 and may drive its overactivity in depression. This led them to the claustrum, two thin neuronal sheets, each one seated near the level of the temples. It's a small but mighty structure, regulating important functions like cognition, the influx of sensory information, and sleep. Research has shown that people with depression have a thinner claustrum than people who aren't depressed.

"The human claustrum expresses genes associated with depression, and its activity is altered across multiple neuropsychiatric disorders," adds Feng, noting that he and his lab wanted to tease out the signaling between the claustrum and Area 25 to better understand how it might be implicated in depression.

The human claustrum expresses genes associated with depression, and its activity is altered across multiple neuropsychiatric disorders.

> **By identifying specific neural circuits within the thalamic reticular nucleus, and showing how their dysfunction can produce symptoms, we may finally detail the neurobiology behind ADHD.**
>
> **–GUOPING FENG**

In their recent studies, the scientists used chemogenetics to boost the activity of the pathway between the claustrum and Area 25 in the brains of marmosets. This modification led to depressive symptoms in the animals, including reduced motivation and physical activity. Then, when the researchers inhibited activity between these two regions in "low-mood" marmosets, their motivation and physical activity improved.

Feng's team is finally excavating the hidden workings of the brain to reveal the neural wiring of depression. In exploring this circuit further, they aim to gain deeper knowledge of Area 25 and its connections — and eventually find more effective strategies to treat depression.

Unraveling ADHD

Attention-deficit hyperactivity disorder (ADHD) affects about eight percent of children, yet, 20 percent of patients do not respond to current treatments. If there were a way to act directly on the neural culprits driving ADHD, this would tremendously transform the treatment landscape — but these brain circuits have remained concealed from scientists' view.

Some studies suggest that ADHD may be linked to problems in the thalamic reticular nucleus (TRN), a brain structure involved in sensory processing and attention. It serves as the doorman of the thalamus, responsible for controlling which sensory signals can travel to the cortex, letting some information in and blocking other signals out. If the TRN region slips in vigilance, it could flood the brain with information that leads to ADHD symptoms.

"People with ADHD can experience sensory overload — feeling overwhelmed by ordinary sights, sounds, or touches — and they may have difficulty filtering thoughts and controlling impulses," says Feng. "By identifying specific neural circuits within the TRN, and showing how their dysfunction can produce symptoms, we may finally detail the neurobiology behind ADHD."

The Feng lab revealed two distinct subnetworks within the TRN in a study published in *Cell Reports* in December 2024. They leveraged genetic mouse models, brain-mapping techniques, and brainwave recordings to discover that each TRN subnetwork has unique connections and functions: one mainly handles incoming sensory signals, while the other regulates complex cognitive thinking. "When we disrupted each TRN subnetwork in mice, this led to issues with sensory processing and atypical brain activity patterns, mirroring issues seen in psychiatric disorders like ADHD," explains Feng.

By zeroing in on these TRN subnetworks, the researchers aim to crack open their intricate circuits and detect exactly where brain systems go awry in ADHD, paving the way for more effective treatments that target the disorder at its source.

Gene Therapy and Therapeutic Development

To treat a host of conditions—including severe brain diseases and disorders—the labs of Feng Zhang and Guoping Feng continue to craft remarkable molecular tools and gene therapies that are propelling cutting-edge treatments.

Devising novel genome-editing methods

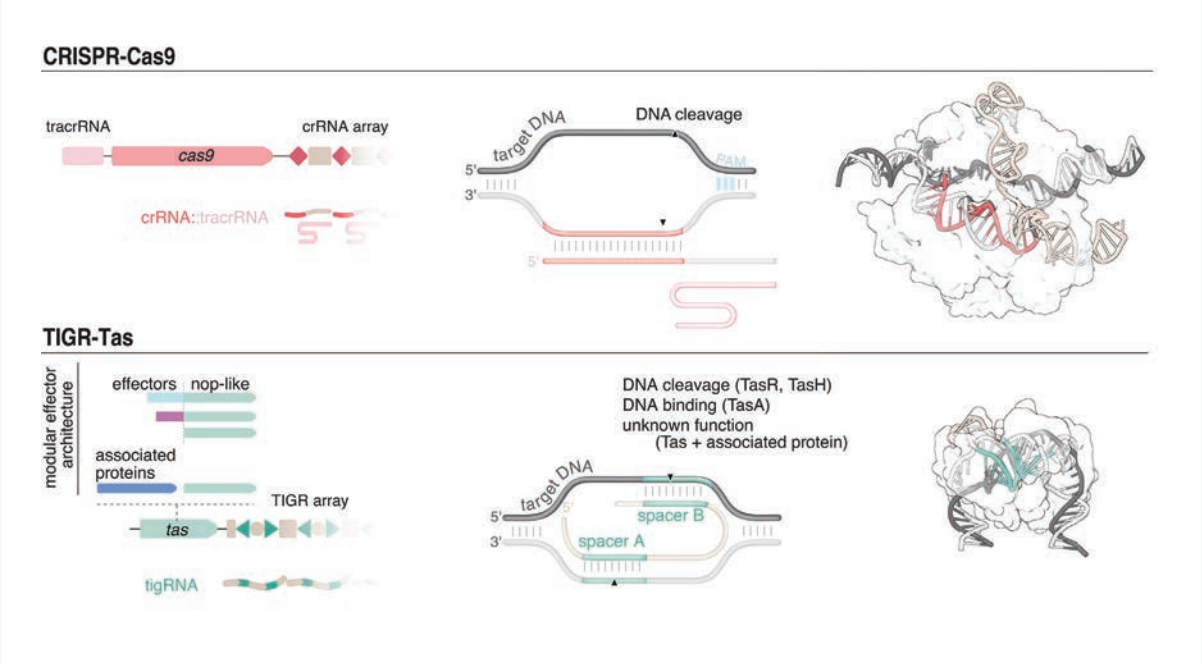
Genome-editing tools have opened new possibilities for treatments that target the root causes of diseases and disorders at their genetic source. Recently, in a tremendous breakthrough, the lab of Feng Zhang—the James and Patricia Poitras Professor of Neuroscience at MIT—has once again expanded the suite of genome-editing technologies.

The lab's latest Tandem Interspaced Guide RNA (TIGR) systems, equipped with TIGR-associated (Tas) proteins, elevate the current state of molecular tools. These systems are far more compact than existing methods and can be programmed to target any desired DNA sequence, making them highly adaptable for more precise and effective delivery in the body.

Zhang says that TIGR-Tas systems could overcome some limitations of CRISPR-based tools. "CRISPR systems can only target portions of DNA that are bordered by specific sequences. TIGR doesn't need these sequences to operate successfully," says Zhang. "Therefore, TIGR-Tas systems should be able to edit any location in the genome. These modular platforms may be the most customizable tools in the genome-editing space to date."

Like CRISPR systems, TIGR systems find their target DNA through a guide RNA that can be reprogrammed to match the DNA site of interest. However, in TIGR systems, the three-part interaction between the Tas protein, the guide RNA, and the target DNA is distinct from CRISPR systems. This offers new avenues for precision targeting, particularly in the context of modular editing tools that rely on TIGR for targeting DNA but use another protein for editing it, as in the case of base editors.

"To develop TIGR-Tas, we pinpointed the exact component of CRISPR-Cas9 that binds to an RNA guide and analyzed the domains that enable this feature," explains Zhang. Then, using a large language model for proteins, the researchers scoured massive databases for other proteins that might share a similar function. This led them to a class of proteins that use an RNA guide component: TIGR-Tas systems.



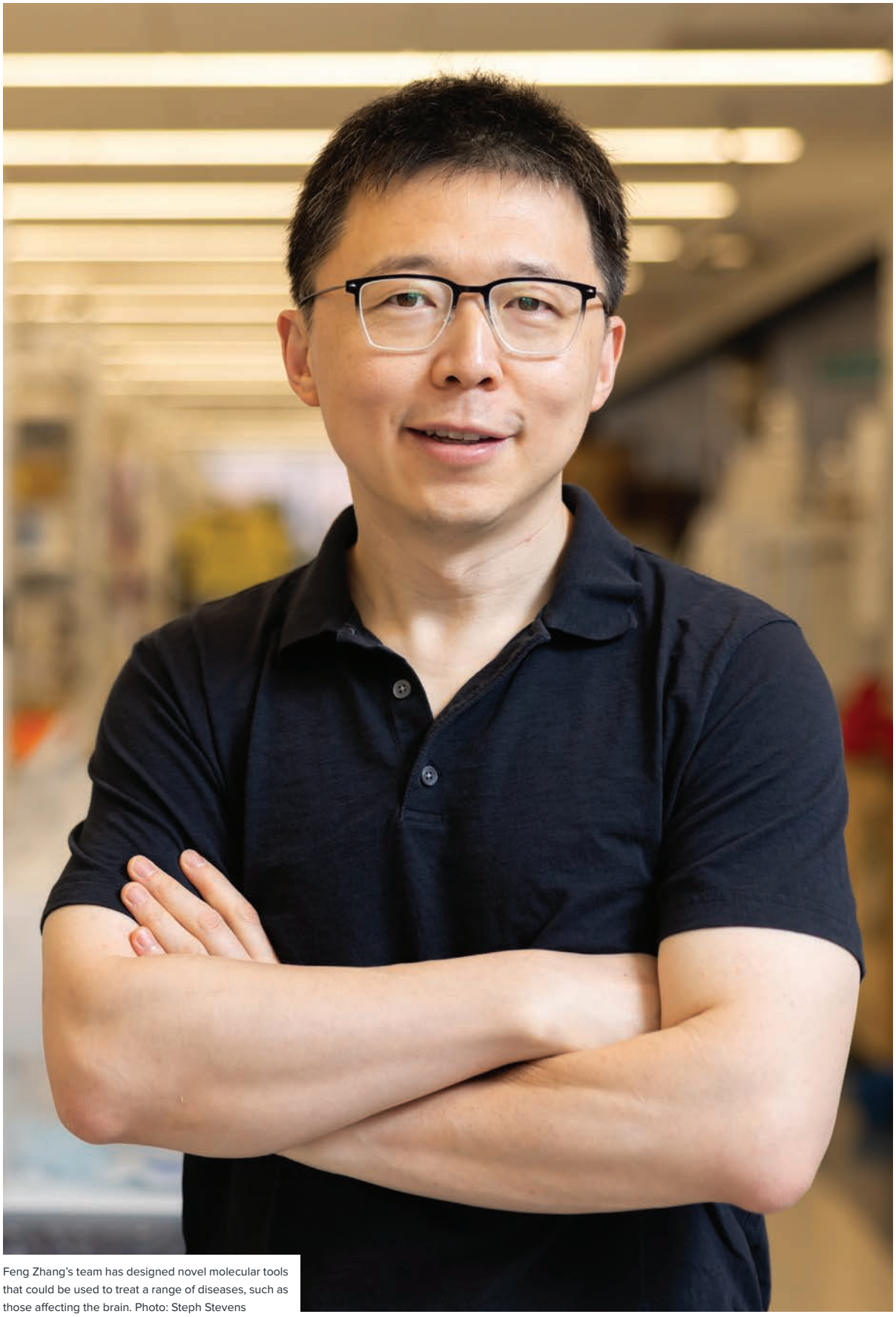
The new Tandem Interspaced Guide RNA (TIGR) systems developed by the Zhang lab are far more compact than previously discovered tools like Cas9 and can be programmed to target any DNA sequence. Image: Zhang lab

Over 20,000 unique Tas proteins emerged from the Zhang lab's search, most of which are found in viruses that infect bacteria. The Zhang lab researchers were excited to find that some of these Tas proteins could edit human DNA.

Tas proteins are about one-quarter the size of Cas9, meaning that they can be more easily packaged into delivery vehicles. "Not only is creating flexible, efficient, and precise genome-editing systems a great challenge, but fitting them onto transport vessels has also been a long-standing hurdle," says Zhang. The team plans to explore the potential of these systems more deeply so that researchers can devise new TIGR-based methods that enhance current therapeutic approaches.

"TIGR-Tas systems should be able to edit any location in the genome. These modular platforms may be the most customizable tools in the genome-editing space to date."

–FENG ZHANG



Feng Zhang's team has designed novel molecular tools that could be used to treat a range of diseases, such as those affecting the brain. Photo: Steph Stevens

A gene therapy for a complex brain disorder gets closer to reaching clinics

In an outstanding achievement from the lab of Guoping Feng, the James W. (1963) and Patricia T. Poitras Professor of Neuroscience at MIT, a gene therapy targeting *SHANK3* mutations has entered clinical trials. *SHANK3* gene mutations can lead to profound autism and Phelan-McDermid syndrome, a severe neurodevelopmental disorder. This scientific triumph is a notable one to come from the Feng lab.

Feng explains that most patients with *SHANK3* mutations are missing a functional copy of the gene, known as haploinsufficiency. "In individuals with *SHANK3* haploinsufficiency, neuronal signaling at synapses is weakened, leading to severe neurodevelopmental challenges," he says. The Feng team created a therapy that remedies this deficit by introducing a working copy of the gene to put synaptic function back on track.

In 2024 — after several years of rigorous de-risking and promising research results — the therapy was licensed to Jaguar Gene Therapy, a biotechnology company, for clinical development. "Jaguar has started to administer this gene therapy to pediatric patients with *SHANK3* mutations. We are beyond excited that it has reached this point in the development pipeline, and we're hopeful that it will significantly improve the quality of life for these patients," says Feng.

People with *SHANK3* mutations are currently deprived of a cure, and this promising therapy could lay the groundwork for other gene therapies that can treat complex brain disorders. Feng believes that with continued scientific and clinical progress, his team's gene therapy may one day be a potential way to treat major mental illnesses as well.

Creating CRISPR enzymes that dodge the immune system

CRISPR-based technologies hold immense power in correcting disease-causing mutations in genes. However, because these systems are derived from bacteria, some of their components can trigger strong immune responses in humans. If gene therapies that use CRISPR are detected and disarmed by the immune system, this could prevent them from delivering their therapeutic cargo and might even cause adverse side effects.

The Zhang lab reached a remarkable milestone this year: They engineered CRISPR enzymes that can evade the immune system while maintaining strong gene-editing abilities. This research was published in January 2025 in *Nature Communications* and unveils a new genre of CRISPR-based tools that may be safer and more effective than existing methods.

"We achieved this breakthrough by focusing on two CRISPR nucleases, Cas9 and Cas12 — enzymes that cleave DNA," says Zhang. He and his team applied advanced mass spectrometry to pinpoint three short DNA sequences in each nuclease that could trigger an immune response. Until this research, scientists didn't know which parts of Cas9 and Cas12 were identified by the immune system.

The team then collaborated with Cyrus Biotechnology — a company that uses computational tools to design immune system-evading proteins — to defang these nucleases and design revised versions that did not contain those newly implicated sequences. "Our team engineered several versions of the enzymes, selected the most promising ones, and tested them in mouse models and human cells. We were pleased to find that these modified nucleases could cut DNA with high efficiency while tremendously reducing the immune response sparked by the initial nucleases," Zhang explains. Not only does this work enhance the safety of CRISPR-based therapeutics, the first of which was approved for clinical use in late 2023, but it also provides a roadmap for engineering other potentially therapeutic proteins that can evade an immune response.

NovaIscB: the newest RNA-guided enzyme

Zhang and his lab have remained vigilant in their mission to create an arsenal of powerful genome-editing tools. In a recent study published in *Nature Biotechnology*, the researchers engineered a bacterial RNA-guided enzyme to edit human DNA: NovaIscB.

NovaIscB is the cutting-edge product of several years of meticulous research. Back in 2021, the Zhang lab discovered a class of proteins called OMEGAs, including a variant known as IscB. IscBs are enzymes that can edit DNA at precise locations using RNA as a guide. This is similar to Cas9 — in fact, Cas9 is a descendant of IscBs. If you imagine a gene-editing system as a vehicle, the IscB enzyme is the driver that directs the system to a target DNA sequence. By reprogramming the driver to route to various destinations, scientists should be able to target any sequence in the genome.

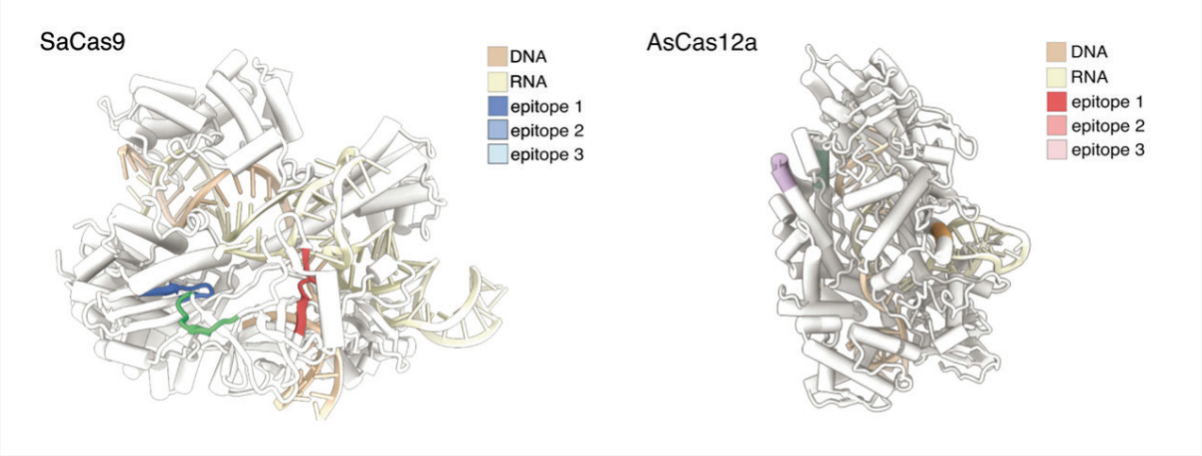
IscBs are about a third of the size of Cas9, making them more suitable for small transport vessels — such as adeno-associated viruses — for precise delivery. Zhang and colleagues saw the power of IscBs but knew that they still needed to be refined for effective use in human cells.

The Zhang team analyzed 400 IscB enzymes, and from this pool, culled 10 candidates that could edit human DNA. "We wanted to adapt these enzymes for optimal use in human cells. However, doing so is a delicate process," explains Zhang. Boosting the activity of the enzymes enhances their function in human cells, he says, but if overactive, the enzymes could cut DNA at sites outside of the target location.

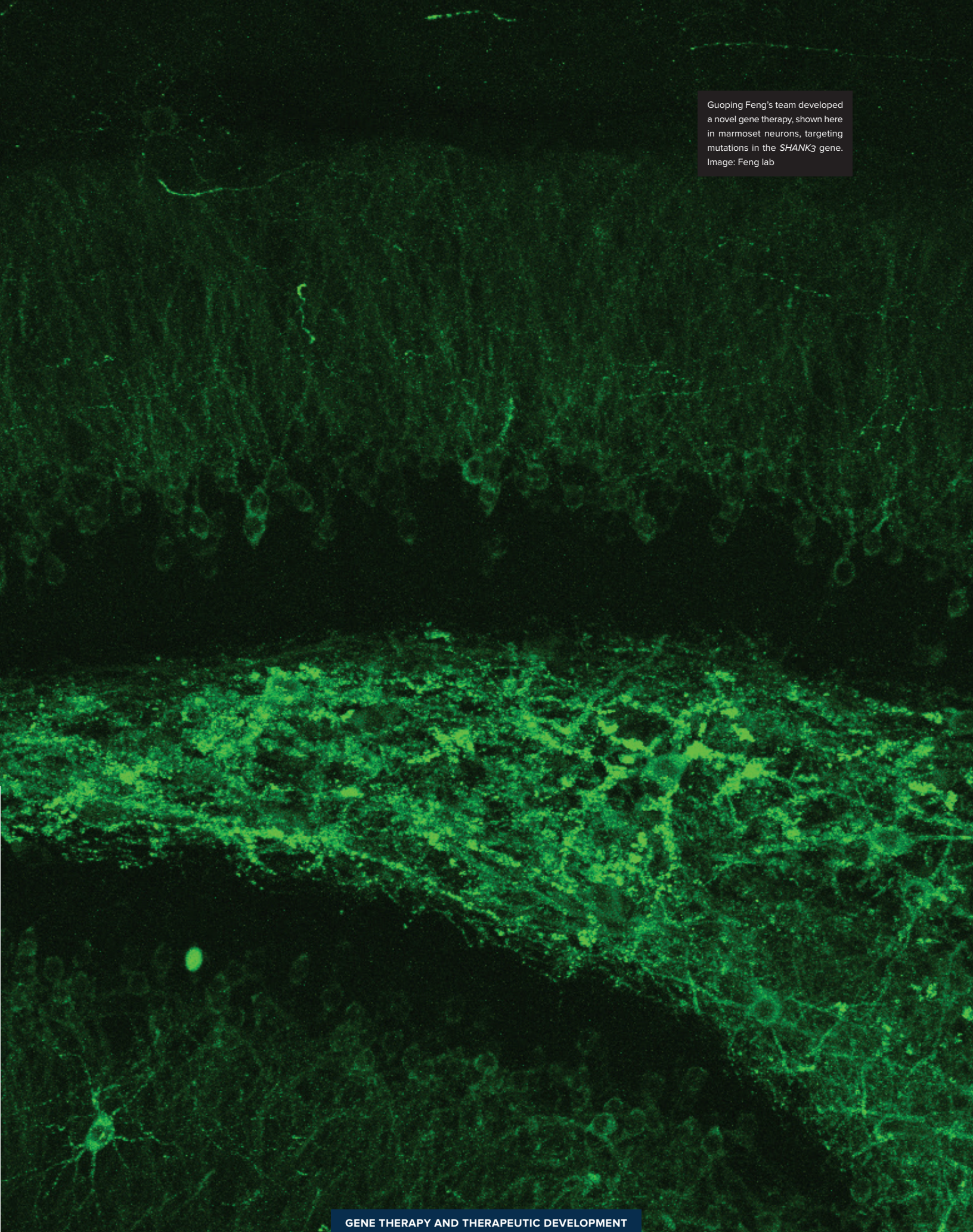
To engineer new proteins, such as an optimal IscB, a common practice in the field is to induce random alterations in a protein and observe the downstream effects. But this is painstaking and time-consuming work. "AlphaFold2 — an advanced computational tool — uses artificial intelligence to predict the effects of a particular change in a protein. It helped drastically streamline our work and pointed us toward developing an optimized version of IscB," explains Zhang.

That version is NovaIscB, demonstrating high specificity and having 100 times greater activity in human cells than the original IscB protein. Using this highly active and specific variant, Zhang's team created a gene-editing tool that represses gene expression, a promising therapeutic strategy to turn off a gene that is either malfunctioning because it contains mutations or is operating in a pathological context. The team demonstrated that this tool, called OmegaOFF, can be used in mice to significantly reduce the expression of a gene involved in cholesterol synthesis to lower cholesterol levels.

The scientists now intend to refine these technologies and their other innovative tools for novel treatments — potentially those that can treat psychiatric diseases — and unlock fresh frontiers in the therapeutic landscape.



In a breakthrough study, the Zhang lab engineered CRISPR enzymes — derived from enzymes Cas9 and Cas12 — that can evade the immune system. Image: Zhang lab



Guoping Feng's team developed a novel gene therapy, shown here in marmoset neurons, targeting mutations in the *SHANK3* gene. Image: Feng lab

PEOPLE

Talented early-career researchers in the Poitras Center are disrupting conventional methods to broaden the scope of psychiatric research.

Cynthia Rais

2024–2026 Poitras Center Postdoctoral Fellow, Harnett lab

Photo:
Steph Stevens

“I aim to find a more precise brain target to improve the use of ketamine for treating various psychiatric diseases. I’m deeply grateful to the Poitras family for supporting my career and this important research.”

Exploring ketamine as a therapeutic agent

Ketamine was first developed in the 1960s. During the Vietnam War, it served as a powerful anesthetic for battlefield surgeries. In recent decades, research focused on ketamine (or a derivative of the drug) has shown its promise in treating suicidal ideation, post-traumatic stress disorder, and severe depression. While scientists' knowledge of ketamine's anesthetic qualities is robust, a full understanding of how it heals the brain — including the neural mechanisms it employs — is lacking.

How does ketamine alter the brain to treat psychiatric illness? Cynthia Rais, the 2024-2026 Poitras Center Postdoctoral Fellow, is embarking on a bold quest to answer this question.

"We still don't know which brain circuits ketamine acts on to elicit therapeutic effects," explains Rais, who seeks to find the cortical areas in the brain that ketamine manipulates when being used to treat severe brain conditions. "I aim to find a more precise brain target to better understand this process and improve the use of ketamine for various treatments. I'm deeply grateful to the Poitras family for supporting my career and this important research," she says.

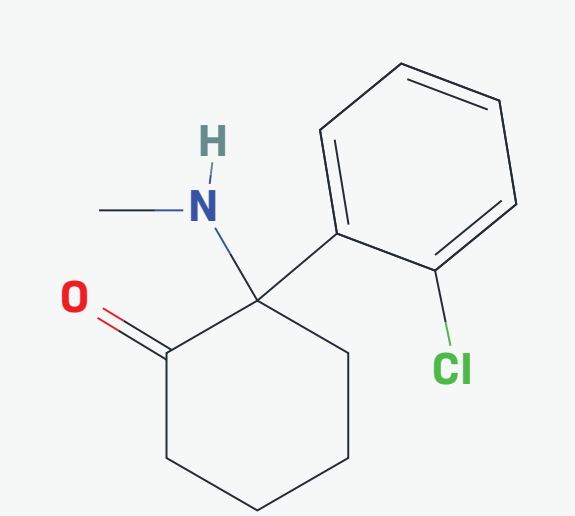
In grade school, Rais was drawn to the mystique of science. "I enjoyed science more than other subjects. In particular, I found biology immensely challenging and complex," she says. This complexity didn't deter Rais — it ignited a deeper fascination. "I wanted to dive into it. Could biology explain why the people around me are so different from each other? I sought to understand the brain — not just the psychological part, but also its molecular and cellular basis."

Rais went on to receive her bachelor's degree in biology and a master's in neuroscience from the University of Bordeaux in France. She later attended the University Medical Center Hamburg-Eppendorf in Germany for her PhD in neuroscience. "During my PhD, I investigated the stability of synapses, signaling junctions between neurons, in the hippocampus. I was also involved in a study that showed the effects of anesthetic doses of ketamine on dendritic spines — wiry extensions that protrude from neurons and enable them to communicate with each other," she says.

The hunt for ketamine's neural mechanisms

That research has equipped Rais to explore how ketamine affects synapses in the lab of McGovern Institute investigator Mark Harnett. "Ketamine blocks NMDA receptors in the brain. Normally, these receptors bind to glutamate, a neurotransmitter that encourages signaling between neurons," Rais explains. By blocking these receptors, ketamine boosts glutamate levels, which triggers the release of dopamine to elevate mood and increase motivation and reward processes.

"We also see that visual neurons in the brain show increased activity with therapeutic doses of ketamine," she adds. Together, these pieces of scientific knowledge are helping Rais complete the puzzle surrounding the brain and ketamine to one day optimize the drug's use for people struggling with debilitating mental health challenges.



Cynthia Rais is investigating how ketamine, its molecular structure here, alters brain activity when used to treat psychiatric conditions.

Gun Ahn

Graduate Student in Brain and Cognitive Sciences, Gabrieli lab

Photo:
Steph Stevens

“We have a lot of information on patient brain-imaging data and demographics, but this isn’t used to treat depression. What if we integrated such data into clinical care to create personalized treatment plans?”

Leveraging AI to transform depression treatments

"In treating depression, frontline medications or therapy only work for about 50 percent of patients—and this is the best of what we have," says Gun Ahn, a PhD student in the lab of John Gabrieli, the Grover Hermann Professor of Health Sciences and Technology and Brain and Cognitive Sciences at MIT. "We have a lot of information on patient brain-imaging data and demographics, but this isn't used to treat depression. What if we integrated such data into clinical care to create personalized treatment plans?"

Ahn is determined to reshape and refine the treatment landscape for depression. By merging machine-learning approaches with clinical and neuroimaging data, he is pioneering precision-based methods that could help heal depression more quickly and effectively than current strategies. He is motivated not only by his empathy for people struggling with depression but also by his firsthand knowledge of the devastation it inflicts.

Like many during the COVID-19 pandemic, Ahn battled mental health challenges and became troubled by depression. "I was a college student at the time. I felt that I was a failure. It's not objectively true, but when you're in that mindset, it feels like the truth," he recalls. Fortunately, Ahn was able to recover from his depression through medical care and persistence. "If I can help people with depression, maybe they will help others struggling too. It's the best thing that I can do—it's a calling," he says.

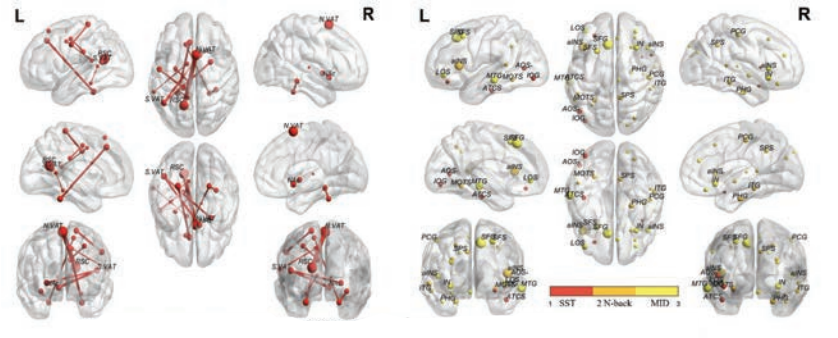
During his first few years at Seoul National University in South Korea for his undergraduate degree, Ahn studied engineering. "But I became more fascinated by humans," he says. "I wanted to study humans in the language of science—and that was through neuroscience." He decided to minor in neuroscience and brain behavior to further explore this field. "Later, I witnessed Google's AlphaGo, an artificial intelligence (AI) model, beat one of the best minds in Go [a Korean strategy board game] at the time. I found this emerging tool alluring," he recalls. This inspired him to also study AI and how the evolving technology can be used to improve human health.

An uncommon journey

Before working to enhance treatments for depression, Ahn studied happiness. He spent a year in Finland in 2019 to study the country's education system as an exchange student. While there, he took note of the social factors that make Finnish people markedly happier than those in other countries, as consistently reported in international studies. "Finland is considered one of the happiest countries in the world. I wanted to learn why their population seems to be happier than most people," he says.

From his perspective, Finland's society has formed a culture that allows people to "fail relatively easily." There, he says, people aren't afraid to challenge themselves. "If they succeed, that's amazing, and if they don't, there's adequate social support so that they can recover and start again," Ahn explains. He went on to write a book on his insights—one of three books he has authored so far.

Ahn believes his unique journey has taught him that the unknown is "not an obstacle, but an opportunity to learn new things." As he works to develop paradigm-shifting treatments for depression, he appreciates how MIT encourages his diverse interests. "Before coming to MIT, people asked me, 'Why are you chasing so many different things?' But here, people value my different passions and my storytelling. I feel like I belong here."



Gun Ahn is integrating important neuroimaging features with machine learning to improve treatments for depression. Image: Gabrieli lab

Yefei Chen

Postdoctoral Fellow, Feng lab

Photo:
Steph Stevens

"During my PhD, I met patients fighting mental health challenges, and I saw how they suffered. That experience has instilled in me a compassion for this human condition. It motivates me to pursue research that can help lessen this suffering."

Exposing a depression-linked brain circuit

Depression affects an estimated 280 million people globally. Yet researchers are still perplexed by how exactly it rewires the brain's connections to induce persistent feelings of sadness and fatigue. Because the disorder manifests differently from person to person, locating one neural circuit that underlies all types of depression has been a formidable scientific challenge.

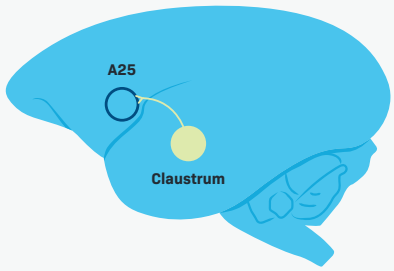
Yefei Chen, though, is intent on finding it. She's a postdoctoral researcher in the lab of Guoping Feng, the James W. (1963) and Patricia T. Poitras Professor of Neuroscience at MIT. "We may be closer to identifying a depression circuit than ever before," says Chen.

In her search for the neural roots of depression, Chen believes that a brain region called Area 25 may be a linchpin in the disorder. This region, present in both humans and primates, facilitates emotion and mood regulation. "Clinical studies discovered that Area 25 is overactive in patients with depression," she says. Moreover, when researchers stimulated Area 25 in primates, this led to depression-like symptoms, such as low physical activity.

"Area 25 communicates with other brain regions, including the claustrum — a small structure with somewhat of a mysterious function. Scientists believe that the claustrum plays a role in attention and other cognitive tasks," Chen explains. "Research has found that this structure is thinner in patients with depression. Therefore, we wanted to test whether the claustrum might contribute to Area 25's hyperactivity, which appears to drive the disorder."

In their investigations, Chen and colleagues in the Feng lab found that when they activated a specific projection between the claustrum and Area 25 via chemogenetics in the brains of marmosets, the animals showed signs of depression, including low mood states and reduced activity.

"This non-human primate animal model can yield valuable insights into depression and offer new avenues for therapeutic development," says Chen. "By identifying how specific brain circuits drive depressive symptoms, we aim to uncover druggable targets that could be the first step in developing more effective treatments," she adds.



Yefei Chen has detected a brain pathway between Area 25 and the claustrum that could unlock new ways to treat depression. Image: Feng lab

A new kind of sleuthing

Chen is using these clues to reach new conclusions on depression. She is used to conducting such detective work, though she now does so a little differently. Before joining MIT, Chen earned her bachelor's degree in forensic medicine and a PhD in forensic psychology at Sun Yat-sen University in China. She pursued basic research on post-traumatic stress disorder during her doctoral studies.

"This work was intriguing, and I decided to focus further on basic neuroscience research," says Chen. However, she noticed the vast gap between basic research and human impact. "There are currently no good genetic models for depression in basic research because it isn't a purely genetic disease," she explains, noting that depression is diagnosed based on people's symptoms, not their genes. "The Feng lab's research with marmosets is what brought me to MIT. It's hard to say if a mouse is depressed. But in primates, there's a wider range of behaviors and neuroactivities that overlap with humans for more translational research."

While Chen seeks to further understand the circuit between Area 25 and the claustrum — and how it could be exploited to treat depression — she leverages tools from her previous training. "In forensic science, you conduct experiments and use logic to organize evidence in a way that answers the question you want to solve." It's not so different from what she does now in studying the brain, she says.

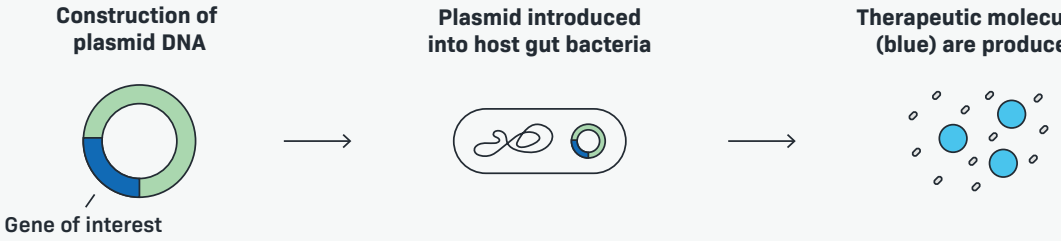
"During my PhD, I met patients fighting mental health challenges, and I saw how they suffered. That experience has instilled in me a compassion for this human condition," says Chen. "It motivates me to pursue research that can help lessen this suffering."

Natalia Quinones-Olvera

Postdoctoral Fellow, Zhang lab

Photo:
Steph Stevens

"My work takes a different approach. Instead of trying to add new bacteria into our gut, I'm reprogramming the ones already thriving inside us."



Natalia Quinones-Olvera uses plasmid engineering to reprogram gut bacteria to produce beneficial molecules.

Reprogramming gut bacteria

When Natalia Quinones-Olvera crafts new molecular technologies, an artist is at work.

She is a postdoctoral fellow in the lab of Feng Zhang, the James and Patricia Poitras Professor of Neuroscience at MIT whose lab has honed powerful gene-editing tools for human use, including CRISPR-Cas9. Quinones-Olvera employs creative methods in the Zhang lab to probe tiny organisms that may be key to thwarting major health threats: gut bacteria.

"The bacteria living in our gut don't just help us digest food. They influence many other aspects of our physiology, including our immune system, metabolism, and our brain," she says. Finding ways to manipulate the microbiome could unlock new treatments for a spectrum of conditions, "from inflammatory bowel disease to diabetes, and even some brain conditions like depression and possibly schizophrenia."

"But there's a problem," she notes. "Introducing helpful bacteria into the gut usually fails because the new strains can't compete with the microbes already living there." If the new bacteria die or dwindle to ineffective levels, as they often do, they cannot exert healing effects.

"Instead of trying to add new bacteria into our gut, I'm reprogramming the ones already thriving inside us," explains Quinones-Olvera. To do so, she is modifying plasmids—circular DNA molecules naturally present in bacteria. Scientists can precisely edit plasmids to carry genes of interest and insert them into existing bacteria such as those living in the gut.

Once an altered plasmid is introduced into a bacterium, the organism uses it as a genetic recipe to make molecules that can correct dysfunctions caused by disease. "By engineering plasmids to carry therapeutic genes, and delivering those plasmids to native gut bacteria, I aim to turn these bacteria into long-term producers of beneficial molecules right where they're needed most," says Quinones-Olvera.

Finding art in science

Quinones-Olvera grew up in Guadalajara, Mexico. Her mother is an artist and designer who sparked an appreciation for art and "elegant things" within Quinones-Olvera at a young age. "I think this helps me view science as a creative art," she says. After falling in love with science in high school, she decided to extend her scientific education at the National Autonomous University of Mexico.

"I initially studied biology in college. But with limited resources in the department, I felt restricted by what I could explore," Quinones-Olvera recalls. She pivoted and studied bioinformatics and computation toward the end of her undergraduate degree; many resources in computational science are freely available online, giving her more freedom to pursue inventive ideas.

Quinones-Olvera initially intended to study computational biology when she began her PhD at Harvard University. "But then I saw all of their abundant resources in molecular science and how creatively the scientists approached research. It made me want to follow that path," she says. She devoted her doctoral degree to studying method development, microbiology, and genomics. "I decided to join the Zhang lab after my PhD—they're experts in biological diversity with a strong focus on human health."

Quinones-Olvera feels that the Zhang lab allows her ingenuity to flourish so she can solve thorny problems that require unconventional thinking. In chasing her goal to reprogram gut bacteria, she is traveling a long road riddled with obstacles—but these are challenges that Quinones-Olvera is prepared to face.

"My mom used to say, 'Creativity is an iterative process—you try something, and then you fix it,'" notes Quinones-Olvera. "Most things don't work the first time. You have to iterate and find branches that lead to successful solutions."

SCIENTIFIC PUBLICATIONS

The Poitras Center's peer-reviewed research amplifies bold new insights into psychiatric illness.

Scientific Publications

Poitras Center researchers are uncovering the biological and genetic roots of serious mental illnesses and developing new treatment strategies ranging from gene therapy to neurofeedback to AI-driven diagnostic tools. Publishing these discoveries in top scientific journals helps spark bold ideas and new collaborations across research, clinical care, and beyond. Below is a summary of the center's publications from spring 2023 to spring 2025.

Evolution-guided protein design of IscB for persistent epigenome editing in vivo.

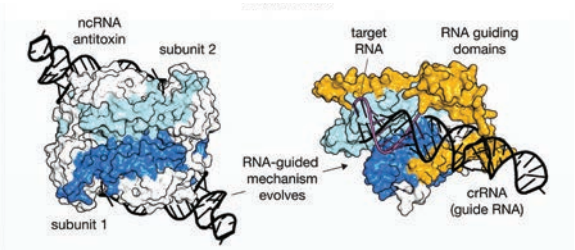
Kannan S, Altae-Tran H, Zhu S, Xu P, Strebinger D, Oshiro R, Faure G, Moeller L, Pham J, Mears KS, Ni HM, Macrae RK, **Zhang F**. | *Nature Biotechnology* (May 2025)

The Zhang team has engineered a powerful, compact gene-editing enzyme that is much more efficient and precise than its natural form; it can even be used to turn off genes in living cells using a single, virus-delivered tool.

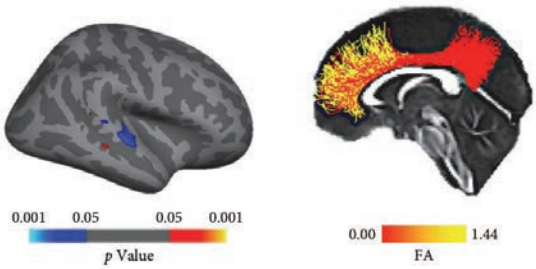
Reprogrammable RNA-targeting CRISPR systems evolved from RNA toxin-antitoxins.

Zilberzwige-Tal S, Altae-Tran H, Kannan S, Wilkinson ME, Vo SC, Strebinger D, Edmonds KK, Yao CJ, Mears KS, Shmakov SA, Makarova KS, Macrae RK, Koonin EV, **Zhang F**. | *Cell* (Apr 2025)

Zhang lab scientists have discovered how the RNA-targeting CRISPR-Cas13 system likely evolved from a bacterial self-defense system, revealing key structural changes that transformed it into a programmable gene-editing technology.



The Zhang lab uncovered the evolutionary history of RNA-guided mechanisms in CRISPR systems. Image: Zilberzwige-Tal et al. From "Graphical Abstract" at https://www.cell.com/cell/fulltext/S0092-8674(25)001035_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867425001035%3Fshowall%3Dtrue



Whitfield-Gabrieli's team found specific brain features that can be targeted to improve auditory hallucinations in schizophrenia via neurofeedback. Image: Whitfield-Gabrieli et al. From Figure 2 at https://pmc.ncbi.nlm.nih.gov/articles/PMC11999755/pdf/DA2025-2848929.pdf

Brain structural and functional neuroimaging features are associated with improved auditory hallucinations in patients with schizophrenia after real-time fMRI neurofeedback.

Zhang J, Tusuzian E, Morfini F, Bauer CCC, Stone L, Awad A, Shinn AK, Niznikiewicz MA, **Whitfield-Gabrieli S**. | *Depression and Anxiety* (Apr 2025)

This new study led by Susan Whitfield-Gabrieli suggests that brain connectivity between regions involved in self-reflection and decision-making may predict who will benefit most from a novel brain-training technique aimed at reducing distressing auditory hallucinations in people with schizophrenia.

Global to local influences on temporal expectation in marmosets and humans.

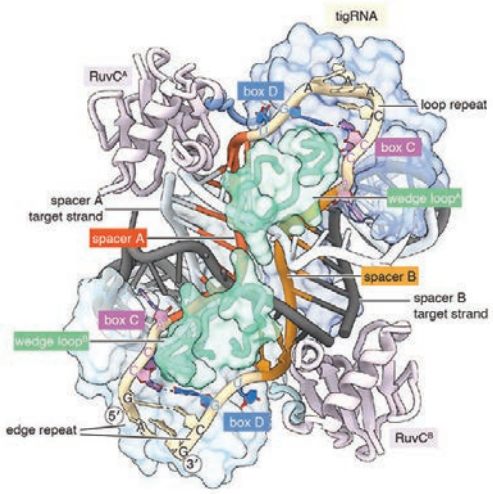
Dragoi T, Sugihara H, Le NM, Adam E, Sharma J, **Feng G**, Desimone R, Sur M. | *Current Biology* (Mar 2025)

Marmosets, like humans, learn to anticipate when events will happen based on past experience. This study led by researchers in the Feng, Desimone and Sur labs shows they continually adjust their expectations using both long-term patterns and recent events — even after they've already learned an effective strategy.

Predicting treatment response to cognitive behavior therapy in social anxiety disorder on the basis of demographics, psychiatric history, and scales: A machine learning approach.

Bukhari Q, Rosenfield D, Hofmann SG, **Gabrieli JDE**, Ghosh SS. | *PLoS One* (Mar 2025)

Using machine learning, the Gabrieli lab demonstrated that answers to a specific anxiety questionnaire called the LSAS can help predict how well someone with social anxiety disorder will respond to therapy — offering a first step toward more personalized treatment.



A new genome-editing system called TIGR-Tas, developed by the Zhang lab, could be more precise and flexible than previous methods. Image: Faure et al. From Figure 6 at https://pmc.ncbi.nlm.nih.gov/articles/PMC12045711/

TIGR-Tas: A family of modular RNA-guided DNA-targeting systems in prokaryotes and their viruses.

Faure G, Saito M, Wilkinson ME, Quinones-Olvera N, Xu P, Flam-Shepherd D, Kim S, Reddy N, Zhu S, Evgeniou L, Koonin EV, Macrae RK, **Zhang F**. | *Science* (Feb 2025)

A group of collaborators led by Feng Zhang uncovered a new family of RNA-guided proteins in phages and parasitic bacteria that can be reprogrammed to very precisely target DNA — even in human cells — offering fresh insights into the evolution and potential of gene-editing tools.

Rational engineering of minimally immunogenic nucleases for gene therapy.

Raghavan R, Friedrich MJ, King I, Chau-Duy-Tam Vo S, Strebinger D, Lash B, Kilian M, Platten M, Macrae RK, Song Y, Nivon L, **Zhang F**. | *Nature Communications* (Jan 2025)

Researchers in the Zhang lab have engineered new versions of CRISPR gene-editing proteins that avoid triggering the immune system while maintaining their full therapeutic power, paving the way for safer treatments of a host of diseases with a genetic root.

Distinct structural and functional connectivity of genetically segregated thalamoreticular subnetworks.

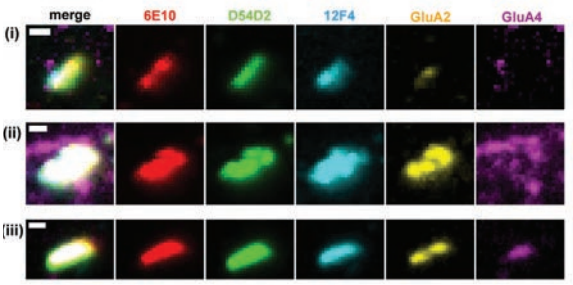
Hartley ND, Krol A, Choi S, Rome N, Levandowski K, Pasqualoni S, Jones C, Tian J, Lee S, Lee H, Kast R, **Feng G**, Fu Z. | *Cell Reports* (Dec 2024)

The Feng and Zu teams discovered two distinct types of neurons in the thalamic reticular nucleus that regulate key aspects of sensory and cognitive processing. The scientists showed that when these circuits go awry, they produce specific brain dysfunctions linked to psychiatric disorders, highlighting their role as a potential target for therapeutics.

Psychiatric symptoms, cognition, and symptom severity in children.

Pines A, Tozzi L, Bertrand C, Keller AS, Zhang X, **Whitfield-Gabrieli S**, Hastie T, Larsen B, Leikauf J, Williams LM. | *JAMA Psychiatry* (Dec 2024)

Susan Whitfield-Gabrieli and collaborators found that the link between mental health symptoms and thinking ability in children changes depending on how severe the symptoms are—helping explain why past research has shown conflicting results.



In the brains of Alzheimer's model mice, the key communication proteins GluA2 and GluA4 tend to cluster together with tiny deposits of amyloid-beta, suggesting a specific disruption in how brain cells communicate. Image: Kang, et al. From Figure 4 https://pmc.ncbi.nlm.nih.gov/articles/PMC11550395/pdf/41467_2024_Article_537hy9029.pdf

Multiplexed expansion revealing for imaging multiprotein nanostructures in healthy and diseased brain.

Kang J, Schroeder ME, Lee Y, Kapoor C, Yu E, Tarr TB, Titterton K, Zeng M, Park D, Niederst E, Wei D, **Feng G**, Boyden ES. | *Nature Communications* (Nov 2024)

Scientists in the Feng and Boyden labs collaborated to develop a new imaging method called multiExR, which allows them to map over 20 proteins at once with nanoscale precision. This novel tool reveals how protein organization in the brain changes in complex disease states.

Phage-triggered reverse transcription assembles a toxic repetitive gene from a noncoding RNA.

Wilkinson ME, Li D, Gao A, Macrae RK, **Zhang F**. | *Science* (Oct 2024)

Feng Zhang and colleagues investigated a bacterial defense mechanism known as reverse transcriptase, revealing that it can convert a noncoding RNA into a toxic protein during viral infection. This surprising strategy allows bacteria to shut down infected cells and block a virus from spreading—a newly uncovered form of genetic regulation.

Structural insights into the diversity and DNA cleavage mechanism of Fanzor.

Xu P, Saito M, Faure G, Maguire S, Chau-Duy-Tam Vo S, Wilkinson ME, Kuang H, Wang B, Rice WJ, Macrae RK, **Zhang F**. | *Cell* (Sept 2024)

The Zhang lab revealed how Fanzor, a gene-editing protein found in many eukaryotes, recognizes and cuts DNA—insights that could help turn it into a powerful tool for future genetic therapies.

Structural determinants of DNA cleavage by a CRISPR HNH-Cascade system.

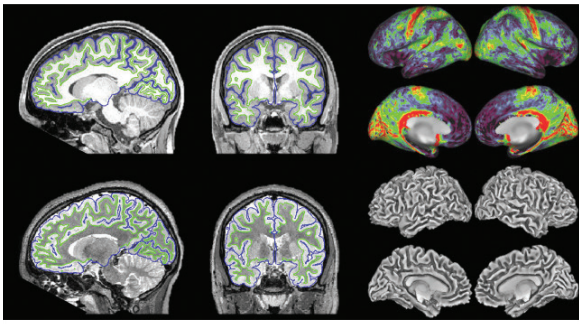
Hirano S, Altae-Tran H, Kannan S, Macrae RK, **Zhang F**. | *Molecular Cell* (Aug 2024)

Zhang lab researchers uncovered the structure of a newly evolved CRISPR system that precisely cuts DNA without the usual helper enzyme. This compact and programmable tool could inspire a new generation of gene-editing technologies.

Targeting the superior temporal gyrus with real-time fMRI neurofeedback: A pilot study of the indirect effects on self-referential processes in schizophrenia.

Morfini F, Bauer CCC, Zhang J, **Whitfield-Gabrieli S**, Shinn AK, Niznikiewicz MA. | *Schizophrenia Research* (Aug 2024)

Working with collaborators at Northeastern and Harvard Medical School, Susan Whitfield-Gabrieli investigated if brain training using real-time MRI feedback may help people with schizophrenia better distinguish their own thoughts from others' voices. Participants who received real-time fMRI neurofeedback targeting the superior temporal gyrus showed increased activity in brain regions linked to self-processing. This finding suggests that this technique can influence broader brain networks involved in self-awareness and auditory hallucinations.



Gabrieli, Whitfield-Gabriel and colleagues used fMRI to reveal how brain circuits involved in anxiety and depression function differently in affected adolescents. Image: Hubbard, et al. From Figure 6 https://pmc.ncbi.nlm.nih.gov/articles/PMC11297143/

The Human Connectome Project of adolescent anxiety and depression dataset.

Hubbard NA, Bauer CCC, Siless V, Auerbach RP, Elam JS, Frosch IR, Henin A, Hofmann SG, Hodge MR, Jones R, Lenzini P, Lo N, Park AT, Pizzagalli DA, Vaz-DeSouza F, **Gabrieli JDE**, **Whitfield-Gabrieli S**, Yendiki A, Ghosh SS. | *Scientific Data* (Aug 2024)

This study shares a rich, publicly available brain and mental health dataset from over 200 teens—many with anxiety or depression—to help researchers better understand adolescent mental health and brain development.

Dynamic functional connectivity correlates of trait mindfulness in early adolescence.

Treves IN, Marusak HA, Decker A, Kucyi A, Hubbard NA, Bauer CCC, Leonard J, Grotzinger H, Giebler MA, Torres YC, Imhof A, Romeo R, Calhoun VD, **Gabrieli JDE**. | *Biological Psychiatry: Global Open Science* (Jul 2024)

A team led by John Gabrieli showed that adolescents who are naturally more mindful tend to spend more time in a reliably detectable brain state marked by strong connections between brain networks—offering clues to how mindfulness may protect against anxiety and depression.

Transgenic targeting of *Fcrls* creates a highly efficient constitutively active microglia Cre line with differentiated specificity.

Kaiser T, Dattero J, Li L, Chen M, Jiang M, Harrahill A, Butovsky O, **Feng G**. | *eNeuro* (Jul 2024)

The Feng lab created a new genetically engineered mouse that allows scientists to precisely modify microglia—the brain's immune cells—without affecting other similar cell types, enabling better studies of brain health and disease without the need for drug-based activation.

Internal initiation of reverse transcription in a Penelope-like retrotransposon.

Frangieh CJ, Wilkinson ME, Strebinger D, Strecker J, Walsh ML, Faure G, Yushenova IA, Macrae RK, Arkhipova IR, **Zhang F**. | *Mobile DNA* (June 2024)

In this study, scientists in Feng Zhang's lab investigated how a rare genetic element known as a Penelope-like element (PLE) moves within the genome, revealing previously unknown mechanisms distinct from other retrotransposons.

Human paraneoplastic antigen Ma2 (PNMA2) forms icosahedral capsids that can be engineered for mRNA delivery.

Madigan V, Zhang Y, Raghavan R, Wilkinson ME, Faure G, Puccio E, Segel M, Lash B, Macrae RK, **Zhang F**. | *Proceedings of the National Academy of Science* (Mar 2024)

The Zhang team discovered that a human protein derived from ancient viruses can be engineered to form tiny capsules that deliver RNA into cells—offering a novel way to develop gene-based therapies.

Neural and cognitive predictors of stimulant treatment efficacy in medication-naïve ADHD adults: A pilot diffusion tensor imaging study.

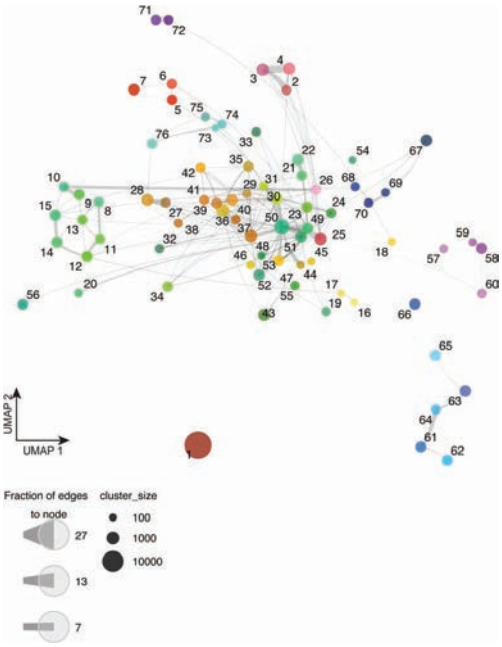
Hung Y, Green A, Kelberman C, Gaillard S, Capella J, Rudberg N, **Gabrieli JDE**, Biederman J, Uchida M. | *Journal of Attention Disorders* (Mar 2024)

This study conducted by the Gabrieli lab and collaborators at MGH found that specific neural and cognitive markers can help predict which adults with ADHD are more likely to benefit from stimulant medications.

Simultaneous two-photon imaging and wireless EEG recording in mice.

Kim B, Ding W, Yang L, Chen Q, Mao J, **Feng G**, Choi JH, Shen S. | *Heliyon* (Feb 2024)

A team of researchers including Guoping Feng and postdoc Qian Chen developed a wireless system that combines EEG with high-resolution brain imaging to reveal how individual neurons behave differently from overall brain activity—especially during changes in consciousness.



McGovern researchers helped map spinal projecting neurons that are critical to the brain-body interplay, as shown by this plot. Image: Winter, et al. From Figure 7 https://pmc.ncbi.nlm.nih.gov/articles/PMC10719099/

A transcriptomic taxonomy of mouse brain-wide spinal projecting neurons.

Winter CC, Jacobi A, Su J, Chung L, van Velthoven CTJ, Yao Z, Lee C, Zhang Z, Yu S, Gao K, Duque Salazar G, Kegeles E, Zhang Y, Tomihiro MC, Zhang Y, Yang Z, Zhu J, Tang J, Song X, Donahue RJ, Wang Q, McMillen D, Kunst M, Wang N, Smith KA, Romero GE, Frank MM, Krol A, Kawaguchi R, Geschwind DH, **Feng G**, Goodrich LV, Liu Y, Tasic B, Zeng H, He Z. | *Nature* (Dec 2023)

Collaborators from MIT, Harvard Medical School, Allen Institute, and UCLA created the first comprehensive map of neurons that send signals from the brain to the spinal cord, revealing distinct types of neurons that control precise movements, coordinate whole-body actions, or fine-tune brain-to-body communication.

Conserved and divergent gene regulatory programs of the mammalian neocortex.

Zemke NR, Armand EJ, Wang W, Lee S, Zhou J, Li YE, Liu H, Tian W, Nery JR, Castanon RG, Bartlett A, Osteen JK, Li D, Zhuo X, Xu V, Chang L, Dong K, Indralingam HS, Rink JA, Xie Y, Miller M, Krienen FM, Zhang Q, Taskin N, Ting J, **Feng G**, McCarroll SA, Callaway EM, Wang T, Lein ES, Behrens MM, Ecker JR, Ren B. | *Nature* (Dec 2023)

By analyzing neurons from humans and other species, scientists from MIT, UCSD, Salk Institute, and Washington University found that differences in gene regulation — often driven by ancient genetic elements — help explain how the human brain evolved unique traits, and may also shed light on the genetic roots of neurological diseases.

Uncovering the functional diversity of rare CRISPR-Cas systems with deep terascale clustering.

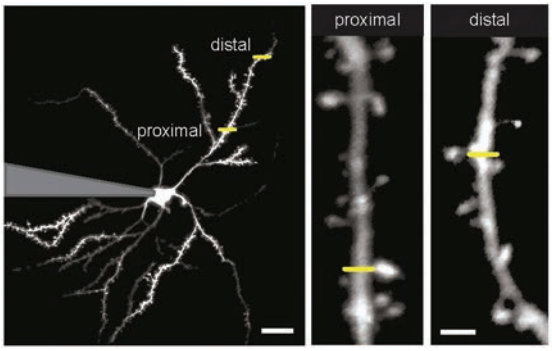
Altae-Tran H, Kannan S, Suberski AJ, Mears KS, Demircioglu FE, Moeller L, Kocalar S, Oshiro R, Makarova KS, Macrae RK, Koonin EV, **Zhang F**. | *Science* (Nov 2023)

By developing a powerful new algorithm to rapidly scan massive genetic databases, the Zhang Lab successfully uncovered nearly 200 previously unknown CRISPR systems — including some with novel genome- and RNA-editing capabilities.

Diversity, evolution, and classification of the RNA-guided nucleases TnpB and Cas12.

Altae-Tran H, Shmakov SA, Makarova KS, Wolf YI, Kannan S, **Zhang F**, Koonin EV. | *Proceedings of the National Academy of Science* (Nov 2023)

A team led by Feng Zhang discovered that TnpB, an ancient and highly adaptable RNA-guided enzyme found in bacteria and archaea, has been repeatedly repurposed throughout evolution — including as the ancestor of CRISPR-Cas12. This insight reveals new potential for understanding and harnessing RNA-guided systems.



Nerve cells called dSPNs are more easily activated in mice that lack a gene known as *SAPAP3*. Image: Malgady, et al. From Figure 4 https://pmc.ncbi.nlm.nih.gov/articles/PMC10872927/

Pathway-specific alterations in striatal excitability and cholinergic modulation in a SAPAP3 mouse model of compulsive motor behavior.

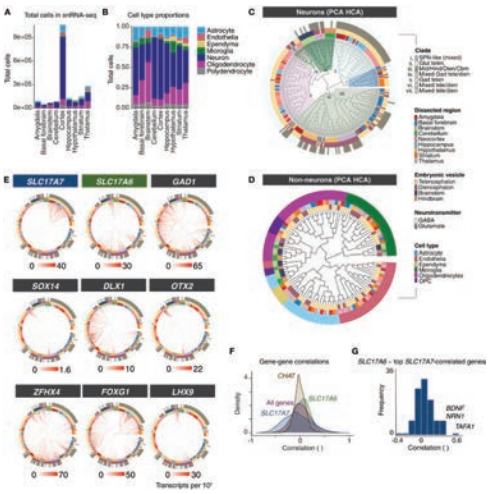
Malgady JM, Baez A, Hobel ZB, Jimenez K, Goldfried J, Prager EM, Wilking JA, Zhang Q, **Feng G**, Plotkin JL. | *Cell Reports* (Nov 2023)

Deleting a gene linked to OCD in mice causes widespread changes in brain circuits that control movement, revealing how disrupted communication and chemical signaling in the striatum may lead to compulsive behaviors.

At-home use of app-based mindfulness for children: A randomized active-controlled trial.

Treves IN, Olson HA, Ozernov-Palchik O, Li CE, Wang KL, Arechiga XM, Goldberg SB, **Gabrieli JDE**. | *Mindfulness* (Nov 2023)

A study conducted by the Gabrieli lab found that children who regularly used a mindfulness app at home for at least 30 days felt less stressed, and their parents noticed fewer signs of negative emotions—suggesting that consistent use of the app can support children's emotional well-being.

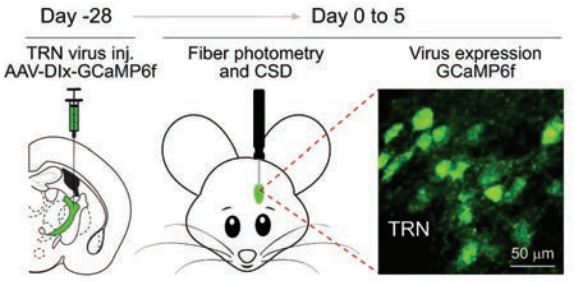


Comprehensive RNA sequencing of the marmoset brain revealed new knowledge of how brain cells become specialized. Image: Krienen et al. from Figure 1 at https://pmc.ncbi.nlm.nih.gov/articles/PMC10569717/figure/F1/

A marmoset brain cell census reveals regional specialization of cellular identities.

Krienen FM, Levandowski KM, Zaniewski H, Del Rosario RCH, Schroeder ME, Goldman M, Wienisch M, Lutservitz A, Beja-Glasser VF, Chen C, Zhang Q, Chan KY, Li KX, Sharma J, McCormack D, Shin TW, Harrahill A, Nyase E, Mudhar G, Mauermann A, Wysoker A, Nemesh J, Kashin S, Vergara J, Chelini G, Dimidschstein J, Berretta S, Deverman BE, Boyden E, McCarroll SA, **Feng G**. | *Science Advances* (Oct 2023)

By analyzing over 2 million neurons in marmosets, a team of scientists led by Guoping Feng found that a brain cell's identity is shaped more by where it comes from during development than by what signals it sends—revealing new insights into how different brain regions are built and function.



The Feng lab used mouse models to explore how chronic sleep disruption affects the way the thalamic reticular nucleus processes pain. Image: Ding, et al. From Figure 3 at https://www.nature.com/articles/s41467-023-42283-6

The endocannabinoid N-arachidonoyl dopamine is critical for hyperalgesia induced by chronic sleep disruption.

Ding W, Yang L, Shi E, Kim B, Low S, Hu K, Gao L, Chen P, Ding W, Borsook D, Luo A, Choi JH, Wang C, Akeju O, Yang J, Ran C, Schreiber KL, Mao J, Chen Q, **Feng G**, Shen S. | *Nature Communications* (Oct 2023)

Chronic sleep disruption can make pain feel worse. This study from Guoping Feng and collaborators at Harvard, Tufts, and UMass shows that a specific brain region involved in sleep and sensory processing—the thalamic reticular nucleus—may drive this effect by losing a natural pain-relieving molecule called NADA.

Mindfulness-based real-time fMRI neurofeedback: a randomized controlled trial to optimize dosing for depressed adolescents.

Bloom PA, Pagliaccio D, Zhang J, Bauer CCC, Kyler M, Greene KD, Treves I, Morfini F, Durham K, Cherner R, Bajwa Z, Wool E, Olafsson V, Lee RF, Bidmead F, Cardona J, Kirshenbaum JS, Ghosh S, Hinds O, Wighton P, Galfalvy H, Simpson HB, **Whitfield-Gabrieli S**, Auerbach RP. | *BMC Psychiatry* (Oct 2023)

Working with collaborators at MGH and Columbia, Susan Whitfield-Gabrieli tested whether a new brain training technique using mindfulness and real-time MRI feedback can help teens with depression by quieting brain networks linked to rumination and negative thoughts.

Cell type-specific delivery by modular envelope design.

Strebinger D, Frangieh CJ, Friedrich MJ, Faure G, Macrae RK, **Zhang F**. | *Nature Communications* (Aug 2023)

Scientists in the Zhang lab developed a new modular delivery system called DIRECTED that uses customizable viral envelopes to target specific cell types—such as human T cells.

Mindfulness supports emotional resilience in children during the COVID-19 pandemic.

Treves IN, Li CE, Wang KL, Ozernov-Palchik O, Olson HA, **Gabrieli JDE**. | *PLoS One* (Jul 2023)

This study led by the Gabrieli lab revealed that children who were naturally more mindful—that is, more adept at staying present and open to their experiences—tended to feel less stressed and emotionally affected by the disruptions of the COVID-19 pandemic.

Reducing default mode network connectivity with mindfulness-based fMRI neurofeedback: a pilot study among adolescents with affective disorder history.

Zhang J, Raya J, Morfini F, Urban Z, Pagliaccio D, Yendiki A, Auerbach RP, Bauer CCC, **Whitfield-Gabrieli S**. | *Molecular Psychiatry* (Jun 2023)

This study led by Susan Whitfield-Gabrieli showed that a personalized brain training technique using mindfulness and real-time MRI can help teens reduce brain activity linked to depression, potentially boosting mindfulness and improving symptoms.

Looking ahead: Advancing new lines of inquiry for impact

Our studies tackling psychiatric disorders continue to yield pivotal findings and unlock potent strategies to treat these conditions. We are thrilled with the Poitras Center's progress to date.

Recent advancements—such as engineering new molecular technologies, decoding severe depression, and honing neurofeedback strategies for schizophrenia—are giving our researchers the momentum they need to propel their work toward real-world impacts. New investigators and their teams will fortify our scientific pursuits by exploring major mental illnesses from fresh angles, including vision-based interventions for mood disorders and the use of ketamine for treating severe depression.

Of course, the progress detailed in this report is just as much the success of the Poitras family as it is ours. Their renewed support will reinvigorate our investigations and push them further toward transforming mental health care. As we forge ahead in our quest to quell psychiatric illness, we remain grateful as ever for the Poitras family's support.

Poitras Center *for*
Psychiatric Disorders Research

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