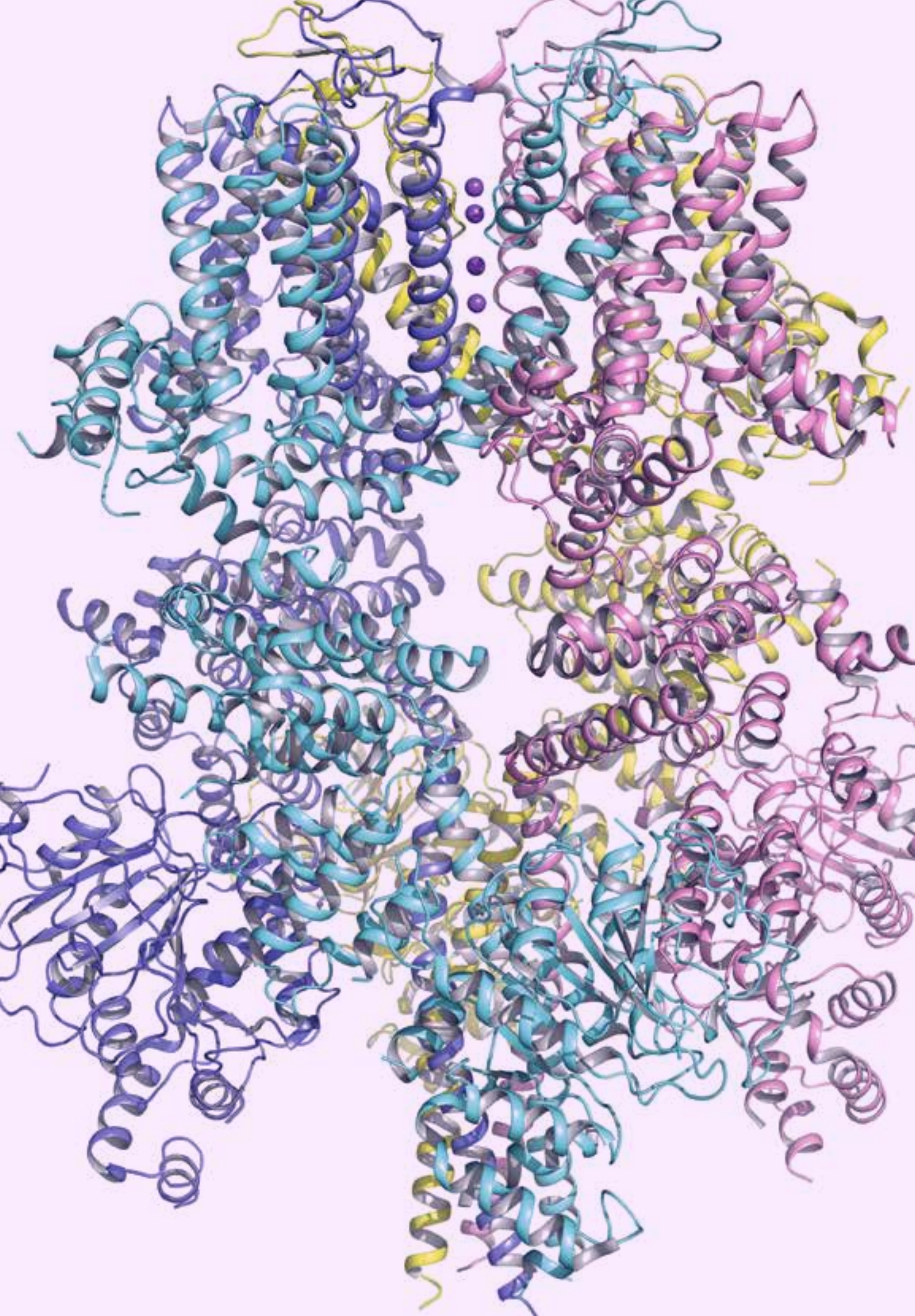
In pursuit of scientific breakthroughs

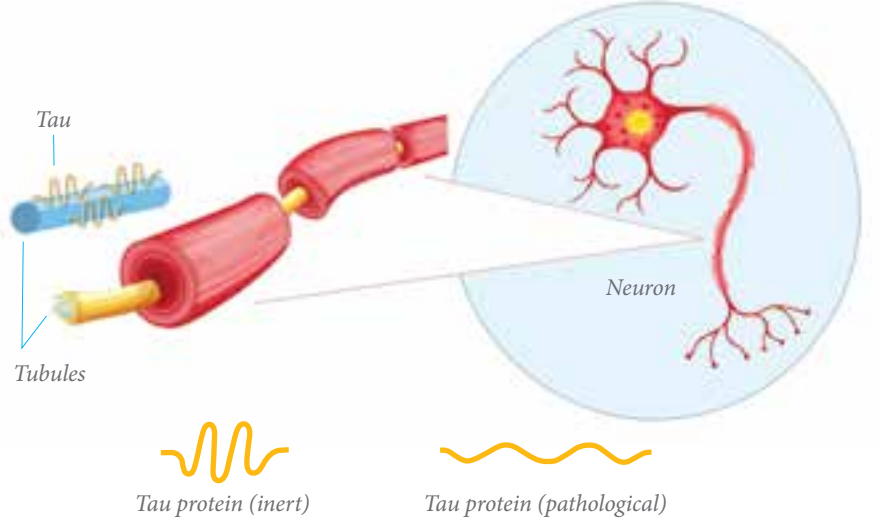
What leads to a breakthrough? Asking tough questions. Digging deeper. Refusing to stop investigating, despite setbacks, until an answer validates a hypothesis. For UT Southwestern researchers, these are ingrained skills that have produced notable findings such as the point at which a protein in the brain turns toxic or the revelation of how a liver hormone affects cravings for alcohol and sugar.

UT Southwestern's cryo-EM facility advances science with its solutions of important protein structures.



Shape-shifting tau identified as genesis of Alzheimer's disease

UT Southwestern scientists have discovered the exact point at which a protein called tau becomes toxic but has not yet begun forming deadly tangles in the brain characteristic of Alzheimer's disease.



In pathological tau, reactive amino acids are exposed, enabling tau to stack up.

This revolutionary investigation – from UT Southwestern's Peter O'Donnell Jr. Brain Institute – provides new insight into the shape-shifting nature of tau just before the molecule begins sticking to itself to form the larger aggregates seen in Alzheimer's cases. The findings reveal a new strategy for detecting the devastating disease before it takes hold, and they also set in motion intense efforts to develop treatments that may stabilize tau proteins before they change shape.

"This is perhaps the biggest finding we have made to date," said Dr. Marc Diamond, Director of UT Southwestern's Center for Alzheimer's and Neurodegenerative Diseases. "It has completely changed how we think about the problem."

The research, published in *eLife,* contradicts the belief that tau has no distinct shape and is only harmful after beginning to assemble with other tau proteins. Scientists in the Diamond lab made their discovery after extracting tau from human brains and isolating the proteins as single molecules. They found that the harmful form of tau exposes a part of itself that is normally folded inside. This exposed portion causes it to stick to other tau proteins, enabling the formation of tangles that kill neurons.

"We think of this as the Big Bang of tau pathology," said Dr. Diamond, referring to the prevailing scientific theory about the formation of the universe. "This is a way of peering into the very beginning of the disease process."

A Professor of Neurology and Neurotherapeutics, and Neuroscience, Dr. Diamond also holds the Distinguished Chair in Basic Brain Injury and Repair. In this study, he collaborated with Dr. Lukasz Joachimiak, an Assistant Professor in the Center for

Dr. Marc Diamond's studies focus on a molecule linked to the beginning of Alzheimer's.

Dr. Diamond is a leading dementia expert credited with determining that tau acts like a prion, an infectious protein that can self-replicate. Prions became notorious as the cause of the 1980s outbreak of mad cow disease.

Alzheimer's and Neurodegenerative Diseases, and in the Department of Biochemistry, who is also an Effie Marie Cain Scholar in Medical Research. Their research was supported by the Rainwater Charitable Foundation, the

The path toward tau research

Growing up, Dr. Marc Diamond pulled apart watches to see how they worked, built small boats and rockets, and held a general fascination with the natural world. The neurologist's leanings toward a future career in science and medicine were inherited as well to some extent – his father, also a neurologist, founded a center for addiction research and two uncles were physicians.

During college, Dr. Diamond worked for two summers in the lab of Dr. Stanley B. Prusiner, a famed University of California, San Francisco researcher who later won the Nobel Prize for discovering infectious proteins called prions.

Dr. Diamond graduated from Princeton University with a history degree – about as far afield from science as you'd imagine – but then headed to UCSF School of Medicine. He took a two-year break as a medical student to work as a Howard Hughes Medical Institute Student Research Fellow in the lab of Dr. Keith Yamamoto, studying how nuclear receptors sense hormones in the body and regulate transcription.

"After working with Keith, I knew I wanted to be a lab scientist," said Dr. Diamond, Director of UT Southwestern's Center for Alzheimer's and Neurodegenerative Diseases, who holds the Distinguished Chair in Basic Brain Injury and Repair. "I decided to focus on neurodegenerative diseases because I recognized that they represent the single most mysterious and awful problem in neurology." At that point, the path to tau research was clear.

After deciding in 2003 to test whether the brain's tau proteins might work like prions to cause neurodegenerative diseases such as Alzheimer's, it took Dr. Diamond seven years to get National Institutes of Health (NIH) funding for his work.

"The ideas were very revolutionary at the time, and we needed tremendous amounts of preliminary data to convince reviewers that this could be true," Dr. Diamond said. Back then, beta-amyloid tangles were the trending Alzheimer's research topic. "Fortunately, we were able to get funding from the Sandler Foundation, a philanthropic supporter of science, to carry on this work."

Later, when he was ready to publish his lab's first work, which reported that assemblies of tau can journey into cells and between them to spread pathology, he spent 18 months getting rejections before his study was finally accepted for publication in the *Journal of Biological Chemistry* in 2009. It is now the most highly cited work from his lab.

National Institutes of Health, and the Effie Marie Cain Endowed Scholarship.

Despite billions of dollars spent on clinical trials through the decades, Alzheimer's remains one of the most devastating and baffling diseases in the world, affecting more than 5 million Americans.

But now Dr. Diamond is hopeful the field has turned a corner, noting that identifying the genesis of the disease provides scientists a vital target to diagnose the condition at its earliest stage, before the symptoms of memory loss and cognitive decline become apparent.

His team's next step is developing a clinical test that can examine a patient's blood or spinal fluid to detect the first biological signs of the abnormal tau protein.

Just as important, efforts are underway to develop a treatment for those diagnosed. Dr. Diamond cites a compelling reason for cautious optimism here: Tafamidis, a recently approved drug, stabilizes a different shape-shifting protein that causes deadly protein accumulation in the heart, similar to how tau overwhelms the brain.

"The hunt is on to build on this finding and make a treatment that blocks the neurodegeneration process where it begins," Dr. Diamond said. "If it works, the incidence of Alzheimer's disease could be substantially reduced. That would be amazing."

Uncharted territory: UT Southwestern joins global effort to map human cells

UT Southwestern's Peter O'Donnell Jr. Brain Institute is taking part in an international effort to map and characterize all cells in the human body, an ambitious project designed to gain insight into how cellular changes cause disease.

Dr. Genevieve Konopka, a neuroscientist with the O'Donnell Brain Institute, leads a seven-member team that is evaluating which technologies are best for determining how genes are expressed in the brain at a single-cell level. The team is discovering how cells turn specific genes on and off to generate the dozens of cell types found in the human brain.

The project is part of the Human Cell Atlas, an effort involving scientists from around the world to create comprehensive maps of all human cells. The goal is to understand how healthy cells work and what malfunctions when people get sick.

Dr. Konopka's brain team is funded by the Chan Zuckerberg Initiative.

"Our project could have a major impact on how we understand and ultimately treat brain disorders with complex genomic underpinnings such as autism and schizophrenia," said Dr. Konopka, Associate Professor of

HUMAN CELL ATLAS

What is the Human Cell Atlas?

In 2016, prominent world scientists launched a project that would describe and define all human cells. As a result, the Human Cell Atlas consortium was founded. The group's goal is to create comprehensive reference maps of all human cells as a basis for both understanding human health and diagnosing, monitoring, and treating disease.

For more information, visit humancellatlas.org.

Neuroscience and a Jon Heighten Scholar in Autism Research, who estimated this work would take at least a decade.

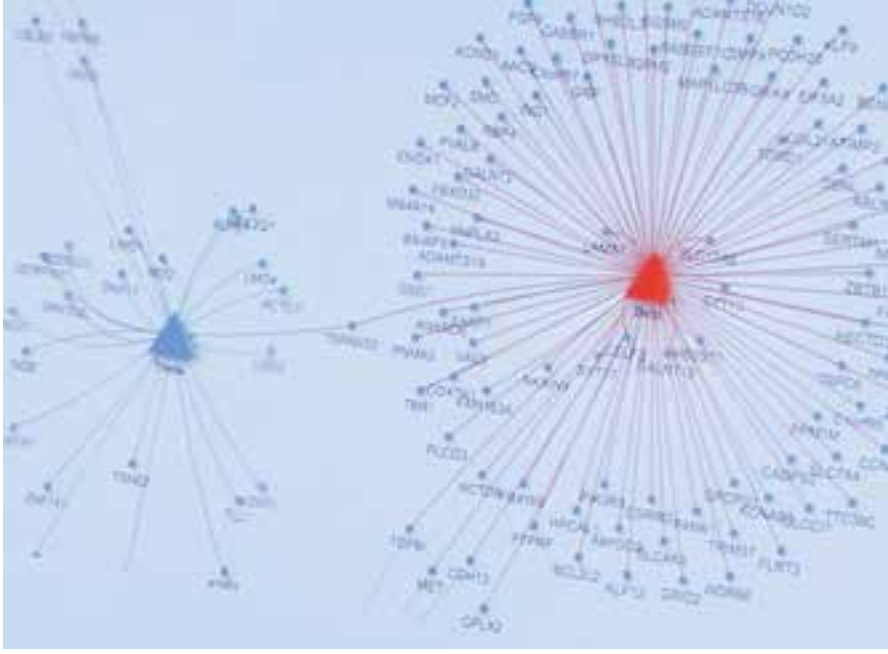
Dr. Konopka has researched various aspects of the brain, including the genetic pathways involved in language development that are vulnerable in autism. In 2017, she published a study identifying more than 100 genes linked to memory.

"Dr. Konopka is a rising star in the field of human gene expression in the brain," said Dr. Joseph Takahashi, Chair of Neuroscience and an Investigator

Dr. Genevieve Konopka, a neuroscientist with the Peter O'Donnell Jr. Brain Institute at UT Southwestern, leads a team working to identify genes and cells within the brain as part of an international project – the Human Cell Atlas – aiming to map all cells in the body.

for the Howard Hughes Medical Institute. Dr. Takahashi also holds the Loyd B. Sands Distinguished Chair in Neuroscience.

The Chan Zuckerberg Initiative, founded by Facebook creator Mark Zuckerberg and his wife Priscilla Chan in 2015, supports various initiatives in scientific research.



The illustration shows genes involved in memory.

Mind bender: Researchers identify 100-plus genes linked to memory

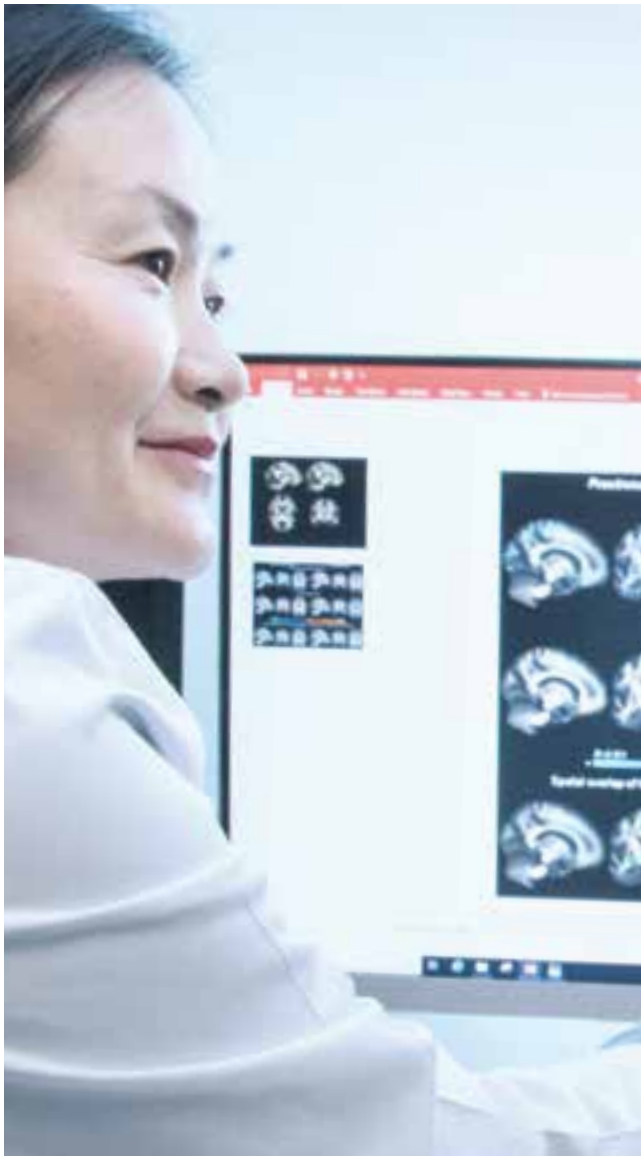
Scientists at UT Southwestern's Peter O'Donnell Jr. Brain Institute have identified more than 100 genes linked to memory, including many previously thought to have no brain process connections.

The findings could ultimately advance treatment of various brain disorders and unravel some of the mysteries behind the body's most complex organ.

Dr. Genevieve Konopka, Associate Professor of Neuroscience and a Jon Heighten Scholar in Autism Research, teamed up with Dr. Bradley Lega, Assistant Professor of Neurological Surgery, Neurology and Neurotherapeutics, and Psychiatry, who was conducting memory research on epilepsy patients. Dr. Lega works with epilepsy patients to map their brain waves and pinpoint patterns related to memory formation. In her research, Dr. Konopka studies the link between specific genes and resting-state brain behavior.

Combining their techniques, the researchers found that a different group of genes is used in memory processing than those involved when the brain is in a resting state.

The researchers are hopeful these findings can help scientists better understand and treat a range of conditions involving memory impairment, from epilepsy to Alzheimer's disease. Follow-up studies are currently underway to refine and add to this list of memory genes by analyzing the expression of genes in the brains of patients undergoing memory assessments.

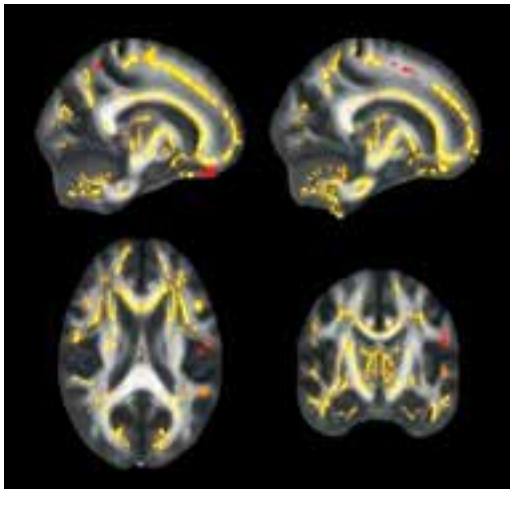


Poor fitness linked to weaker brain fiber, higher dementia risk

Scientists have more evidence that exercise improves brain health and could be a lifesaving ingredient that prevents Alzheimer's disease.

This UT Southwestern research, published in the *Journal of Alzheimer's Disease*, suggests that the lower the fitness level, the faster the deterioration of vital nerve fibers in the brain. What happens then is cognitive decline, including memory issues characteristic of dementia patients.

"This work supports the hypothesis that improving people's fitness may improve their brain health and slow down the aging process," said the study's author, Dr. Kan Ding, an Assistant Professor of Neurology and Neurotherapeutics with the Peter O'Donnell Jr. Brain Institute and a former UTSW fellow and resident.



Brain imaging shows yellow and reddish pixels representing areas where the functionality of white matter is associated with higher fitness levels.

The research focused on white matter, a type of brain tissue comprised of millions of bundles of nerve fibers used by neurons to communicate across the brain.

Dr. Ding's team enrolled older patients at high risk of developing Alzheimer's who showed early signs of memory loss, or mild cognitive impairment. They measured the patients' cardiorespiratory fitness and

Dr. Kan Ding (left) and Dr. Rong Zhang examine images of human brains as part of research at UT Southwestern looking into whether exercise can help ward off dementia.

imaged the brain to test the functionality of their white matter. Memory and other cognitive tests on the patients followed, to evaluate brain function.

The researchers found that lower fitness levels were associated with weaker white matter, which in turn correlated with lower brain function.

In related work, researchers at the O'Donnell Brain Institute are leading a five-year multicenter clinical trial designed to determine whether participating in aerobic exercise regularly and taking medications to reduce high blood pressure and cholesterol levels preserves brain function. This trial involves more than 600 older adults who are at risk to develop Alzheimer's.

Dr. Rong Zhang, Professor of Neurology and Neurotherapeutics and Internal Medicine, is overseeing the trial. The Dallas arm of the study is being carried out by the Institute for Exercise and Environmental Medicine, a joint program between UT Southwestern and Texas Health Resources. Dr. Zhang is Director of the Cerebrovascular Laboratory at the Institute.

UT Southwestern researchers identified a hormone that acts on the brain to increase the desire to drink water in response to specific nutrient stresses that can cause dehydration.

Why alcohol, sugar lead to thirst

Texas and European researchers uncover liver hormone's role in the brain

Why does drinking alcohol or consuming sugar make us thirsty? An international study reveals an unexpected anti-dehydration mechanism that may help in finding new treatments to prevent intoxication.

The study, published in *Cell Metabolism,* identifies a hormone that acts on the brain to increase the desire to drink water under conditions that can cause dehydration, such as alcohol consumption. The study involved research in mice and data from human study participants in Europe.

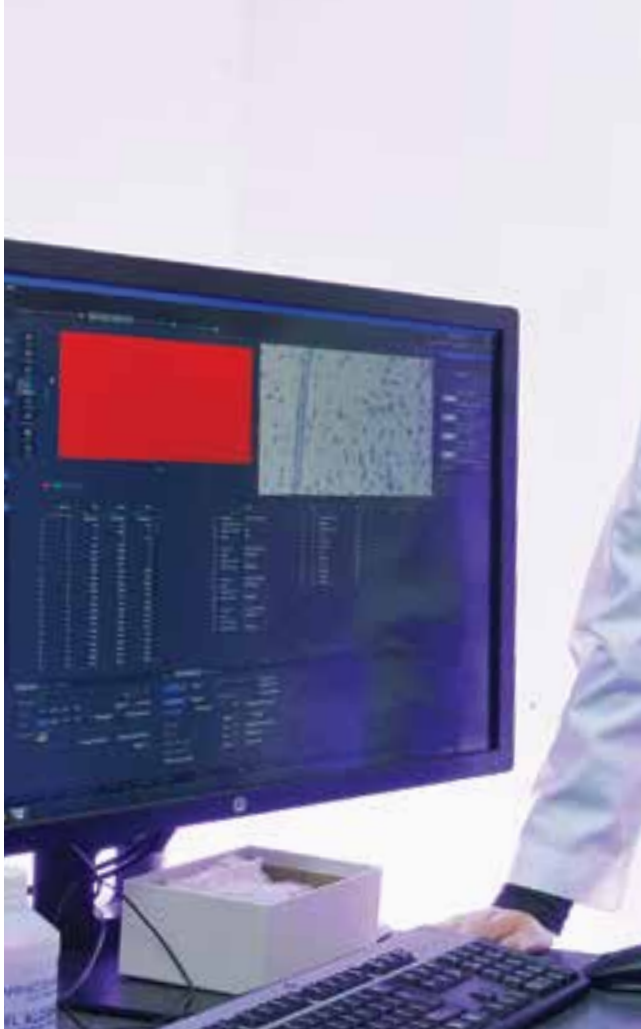
UT Southwestern researchers Dr. David Mangelsdorf and Dr. Steven Kliewer have long studied the liver hormone FGF21, also known as fibroblast growth factor 21. In earlier mouse studies, they found that the hormone acts via the brain's reward pathway to suppress the desire for sugar and alcohol in favor of drinking water.

An important finding in the latest study is a strong response to the hormone in humans as well, Dr. Kliewer said. Validating the researchers' work in mice, 21 study participants at the Medical University of Graz in Austria were randomly assigned to drink either a mixture of alcohol and juice, or juice alone. Hourly over four hours, researchers measured their FGF21 blood levels.

While the hormone remained stable in those drinking only juice, in response to alcohol, FGF21 levels peaked after about two hours.

"This suggests that FGF21 might someday be used as a drug to limit alcohol consumption and protect against its effects in people," said Dr. Mangelsdorf, Chair of Pharmacology, Professor of Pharmacology and Biochemistry, and a Howard Hughes Medical Institute Investigator. Dr. Mangelsdorf also holds the Alfred G. Gilman Distinguished Chair in Pharmacology, and the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology in Honor of Harold B. Crasilneck, Ph.D.

The scientists knew that exposure to alcohol or sugar turned on production of FGF21 in the liver, added Dr. Kliewer, Professor of Molecular Biology and Pharmacology.



Until this study, however, they did not know that the hormone then travels in the blood to a specific part of the brain – the hypothalamus – to stimulate thirst and prevent dehydration.

"Unexpectedly, FGF21 works through a new pathway that is independent of the classical renin-angiotensin-aldosterone thirst pathway in the kidneys," said Dr. Kliewer, who holds the Diana K. and Richard C. Strauss Distinguished Chair in Developmental Biology.

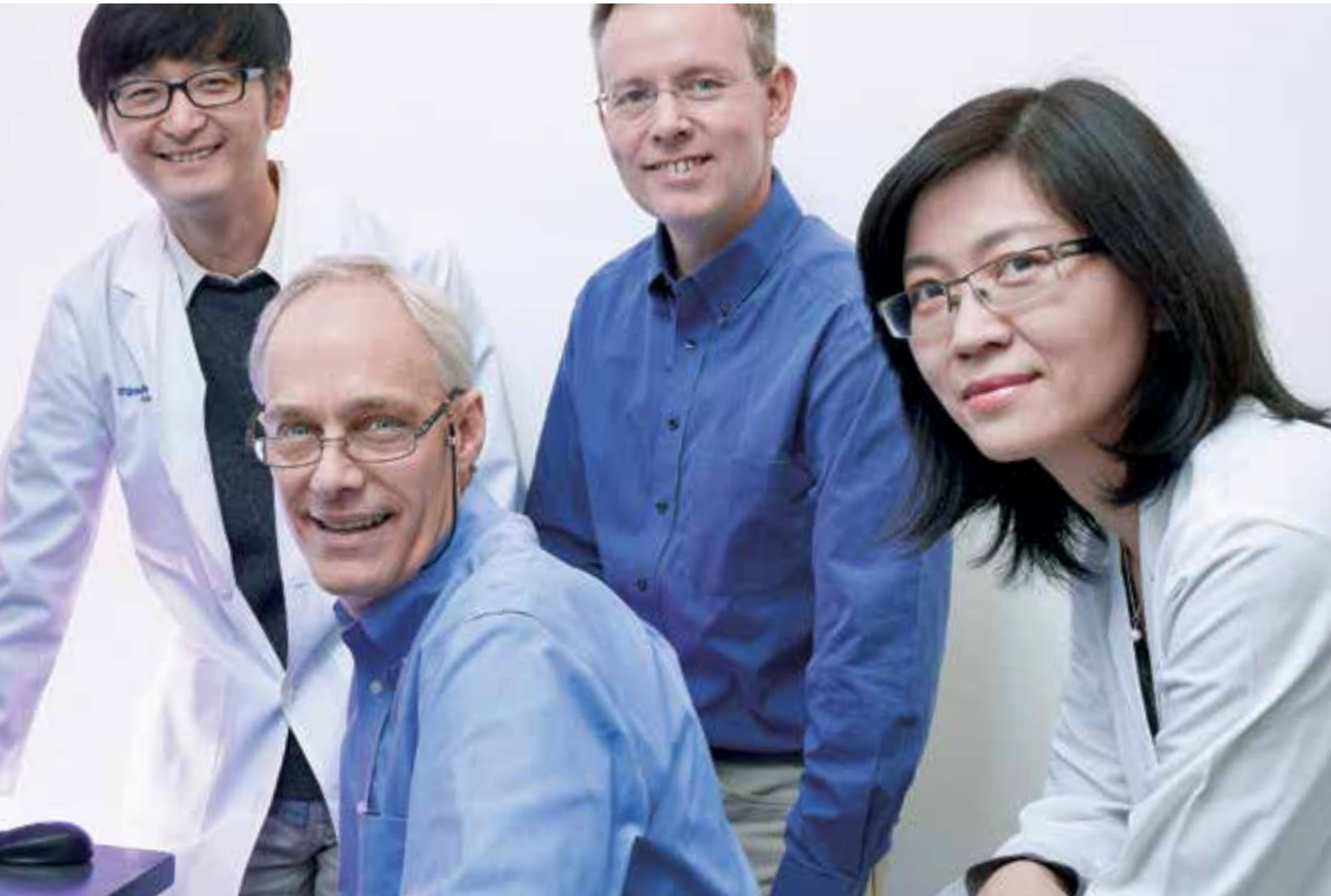
The hormone-induced thirst response appears to depend on another signaling pathway in the hypothalamus, the β-adrenergic circuit, the researchers said.

In another part of the study, done in mice, FGF21 was shown to regulate water consumption in response to nutrient stress. A high-fat/low-carbohydrate diet stimulated water drinking in normal mice, but mice genetically unable to produce the hormone did not drink more in response to this nutritional stress. The findings confirm the hormone's role in signaling the hydration pathway, the researchers said.

For a long time, feeding behavior has been emphasized in metabolic research rather than hydration. This study suggests a change may be on the table, the researchers said.

"To put this in context, we always look at food intake, and the metabolic field has spent comparatively little time studying water intake. This study suggests that we should think more about hydration and how it might contribute to metabolism," Dr. Kliewer said.

UT Southwestern researchers found that the FGF21 hormone appears to reduce cravings for sweets and alcohol. From left: Dr. Parkyong Song, Dr. David Mangelsdorf, Dr. Steven Kliewer, and Dr. Yuan Zhang.



The Nature Index 2018 Annual Tables ranked institutions based on the quality of primary research articles published in 2017, as selected by a panel of scientists independently of Nature Research.

UT Southwestern recognized for quality of scientific research

The quality of scientific investigation underway daily at UT Southwestern and its potential impact is unquestionably high, particularly given the large number of esteemed researchers such as Nobel Laureates, Breakthrough Prize winners, members of the National Academies, and Howard Hughes Medical Institute Investigators who comprise the faculty.

In one of the latest affirmations of this attribute, Nature Index last year ranked UT Southwestern as the top institution within the health care category internationally for publishing high-quality scientific research.

In the Nature Index 2018 Annual Tables, UTSW is ranked first in this category among peer institutions that include Columbia University Medical Center, Memorial Sloan Kettering Cancer Center, Massachusetts General Hospital, and UC San Diego Health. Others rounding out the top 10 are the University of Michigan Health System, MD Anderson Cancer Center, NYU Langone Medical Center, UCLA Health, and Duke University Health System.

"As one of the world's foremost research institutions, UT Southwestern has long cultivated an environment where the pursuit of rigorous scientific research blends seamlessly with multidisciplinary collaboration, resulting in a strong record of leading-edge discoveries and consistent translation into new treatment development," said Dr. Dwain Thiele, Vice Provost and Senior Associate Dean for Faculty Affairs and Initiatives, and Professor, Department of Internal Medicine, who holds the Jan and Henri Bromberg Chair in Internal Medicine.

"This ranking is a testament to the research being conducted every day in the hundreds of labs across campus, where senior faculty, early career researchers, postdoctoral fellows, and graduate students tirelessly work on discovering the underlying causes of disease and the ways in which we can improve health and extend life," he said.

The Nature Index 2018 rankings are based on primary research articles published in a group of 82 high-quality science journals, as selected by a panel of active scientists independently of Nature Research. The list of publications includes both multidisciplinary journals and some of the most highly selective journals within the main disciplines of the natural sciences.

UT Southwestern ranked first among peer institutions in the health care institution category on the Nature Index 2018 Annual Tables.

UTSW researchers solve structure of brain receptor using cryo-EM

Using some of the most advanced cryo-electron microscopy equipment in the world, UT Southwestern scientists have deciphered the atomic structure of an important neurotransmitter receptor in the brain.

In a study published in *Nature,* researchers at UT Southwestern's Peter O'Donnell Jr. Brain Institute provide a detailed description of the structure of the $GABA_A$ receptor – the receptor in the brain targeted by many medications, including the benzodiazepines used for anesthesia during surgery and prescribed to treat epilepsy, anxiety, and insomnia.

The report shows the first 3D atomic structures of the receptor bound to its neurotransmitter GABA and to the drug flumazenil, which is used to reverse anesthesia and to treat benzodiazepine overdoses.

Knowing the structure of the receptor could someday lead to better treatments, said Dr. Ryan Hibbs, Assistant Professor

Dr. Shaotong Zhu (left) and Dr. Ryan Hibbs look over an image of the $GABA_A$ receptor, whose molecular atomic structure they deciphered using cryo-electron microscopy.

Daniel Stoddard, a Core Facilities Manager, shows the Titan Krios cryo-electron microscope to graduate student researcher DaNae Woodard.

of Neuroscience and Biophysics with the O'Donnell Brain Institute.

"This study reveals the first high-resolution structural information for one of the most abundant and important neurotransmitter receptors in the brain," said Dr. Hibbs, an Effie Marie Cain Scholar in Medical Research. "We are tremendously excited about it."

Many drugs – both legal and illegal – work on the $GABA_A$ receptor. The receptor binds to GABA (γ-aminobutyric acid), the major calming neurotransmitter in the adult brain.

To function properly, the brain needs a balance of stimulating and calming signals, Dr. Hibbs said. Dysfunction of the $GABA_A$ receptor is found in conditions marked by excessive excitation in the brain, such as epilepsy.

The $GABA_A$ receptor has been notoriously resistant to structural characterization. X-ray crystallography – a structural biology approach long considered the standard – requires the crystallization of proteins to determine their structures, Dr. Hibbs explained.

Dr. Shaotong Zhu, lead author of the study and a postdoctoral researcher in Neuroscience, tried that method on $GABA_A$ but with inferior results. At the same time, she also tried to unveil $GABA_A$'s structure using cryo-electron microscopy (cryo-EM). That approach was successful, providing the first 3D atomic structures of the receptor bound to GABA and to the drug flumazenil.

This work was made possible using the University's $22.5 million cryo-EM facility, where samples are rapidly frozen to prevent the formation of damaging ice crystals and then viewed at around minus 300 degrees Fahrenheit (cryogenic temperatures). UT Southwestern's facility – which runs around the clock – is one of the world's top facilities for cryo-EM structural biology.

"We were able to define how GABA binds so selectively to the receptor and to explain why drugs like benzodiazepines and flumazenil – the agent that competes with those drugs at the same binding site to reverse their effects – act specifically on this receptor," Dr. Hibbs said.

In addition to the benzodiazepine class of sedatives, the $GABA_A$ receptor is a common target for barbiturates, anesthetics, and alcohol, he added. All of those drugs act on the brain by increasing the activity of the $GABA_A$ receptor, which in turn calms brain activity.

"This receptor is a pharmacological gold mine. However, where these drugs bind and how they exert their effects had not been understood at the structural level," Dr. Hibbs said.

Information about the receptor's structure is just the starting point for determining how it works at a fine level of detail, he added. Next steps include understanding how additional classes of drugs interact with the receptor to change its properties.

"We are particularly curious to examine how ethanol and general anesthetics exert their effects through this receptor. Beyond information on how therapeutic and recreational drugs interact with the $GABA_A$ receptor, we aim to look at how the receptor is held in the right place in neurons in the brain to do its job, which will involve structural analysis of increasingly complex assemblies of the receptor with additional neuronal proteins," Dr. Hibbs said. "The emergent picture will show us how the receptor works and is affected by drugs in a setting approximating its home in the brain."

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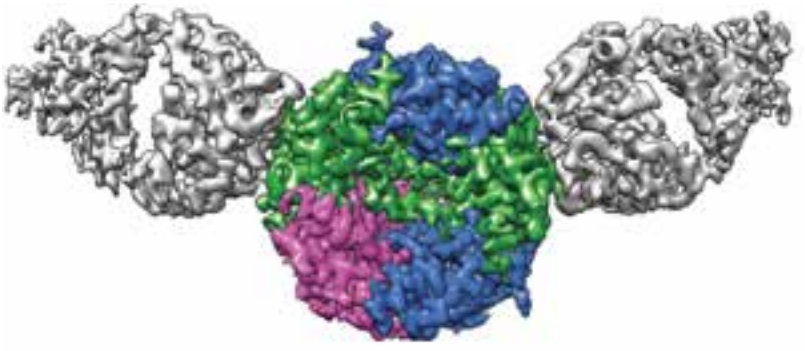


Cryo-EM provided the first detailed 3D atomic structure of the receptor bound to GABA and to the drug flumazenil.

Using the world's most advanced tools in cryo-electron microscopy, UT Southwestern scientists have generated 3D images of atoms and structures within a cell. Here are some of the structures solved to date since the University's $22.5 million cryo-electron microscopy facility opened in 2016.

A The $GABA_A$ receptor – a neurotransmitter receptor that is the target of anti-anxiety drugs like Valium as well as general anesthetics and ethanol

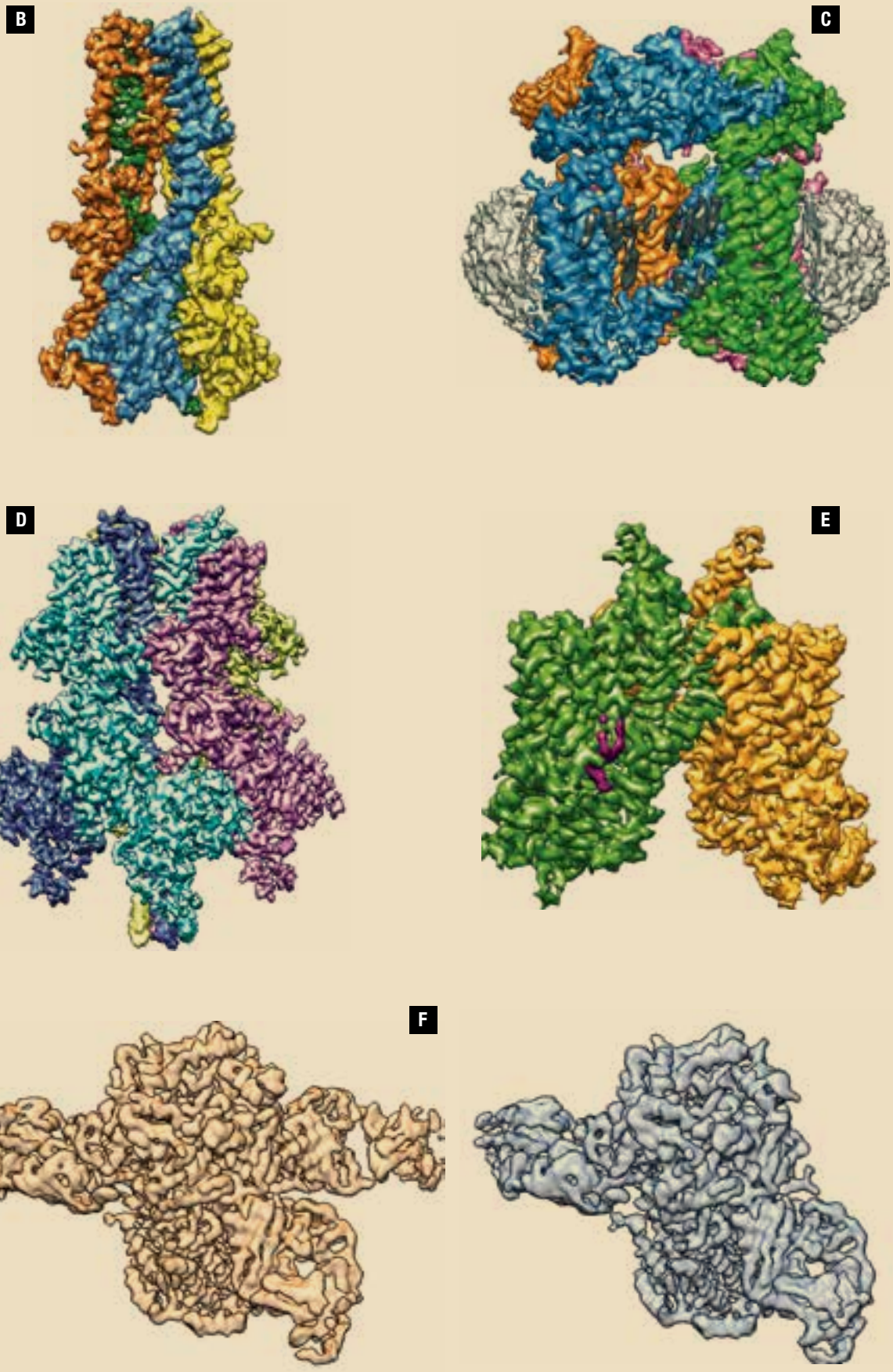
B The mitochondrial calcium uniporter (MCU) – a mitochondrial calcium channel whose function can modulate adenosine triphosphate (ATP) production and cell death

C The TRPML1 ion channel – an ion channel implicated in a rare, inherited human neurodegenerative disease called mucolipidosis type IV

D TRPM4 cation channel protein – a protein with diverse functions in various physiological processes, including temperature sensing

E The TPC1 cation channel protein – a lysosomal ion channel important for nutrient sensing, lipid metabolism, and Ebola virus infection

F The nicotinic acetylcholine receptor (nAChR) – a brain receptor linked to nicotine addiction


B
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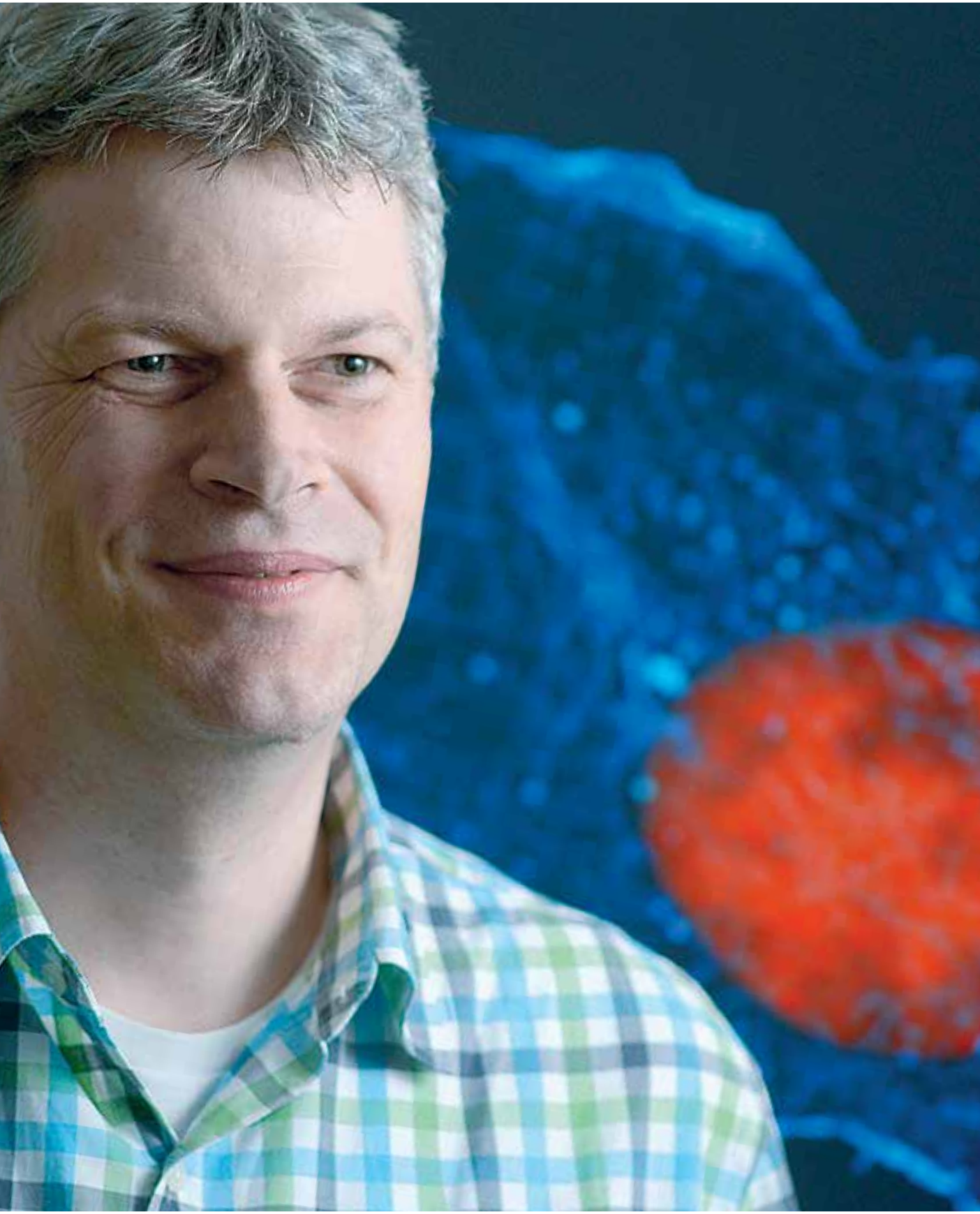
Dr. Gaudenz Danuser, Chair of the Lyda Hill Department of Bioinformatics, wants to build a computer science department within a medical center to help manage and analyze the masses of data now important in biomedical research.



Advancing breakthroughs with the tools of bioinformatics

Dr. Gaudenz Danuser, an internationally recognized leader in engineering and computational biology, has spent the past five years helping UT Southwestern harness the power of bioinformatics – a rapidly growing area of computer science concerned with the collection, organization, and analysis of biomedical data.

Dr. Danuser's goal is to create a computer science department within a medical center – to invent the computational procedures needed to manage and analyze the extremely large data sets now important for biomedical research. Within 10 years, he hopes to recruit 16-20 new faculty involved in this research.

"I see informatics as the backbone of everything we do in biomedical science," said Dr. Danuser, Chair of the Lyda Hill Department of Bioinformatics since its founding. In 2015, a remarkable $25 million gift from Dallas entrepreneur and philanthropist Lyda Hill established the Department.

One of Dr. Danuser's first major studies at UT Southwestern involved designing and building a new microscope capable of creating high-resolution, 3D images of living cancer cells in realistic microenvironments. To do so, he recruited Dr. Reto Fiolka, now Assistant Professor of Cell Biology and Bioinformatics, from the Howard Hughes Medical Institute's Janelia Research Campus. The two co-authored a study in 2016 that describes the design of their unique microscope.

Dr. Danuser also initiated the launch of UT Southwestern's Biomedical High Performance Computing (BioHPC) initiative. Today, the BioHPC has grown into a consortium of 16 UT Southwestern departments that share thousands of processors and 11 petabytes of data storage to perform data-driven basic and clinical science investigations.

In 2015, a $25 million gift from Dallas philanthropist Lyda Hill established the Lyda Hill Department of Bioinformatics.

"Besides assembling increasingly more sophisticated computer algorithms, including artificial intelligence systems, to discover more and more refined information in growing piles of data – which are truly meaningful to biomedical research and clinical practice – I predict that one of the most exciting expansions of bioinformatics moving forward will involve the science of perception," said Dr. Danuser, also Professor of Cell Biology, holder of the Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science, and a Cancer Prevention and Research Institute of Texas Scholar.

"We need to think about how we present the essence of all data we are generating in an intuitive way. Bioinformatics may more and more become the art of finding and seeing the important."