

STARGAZING IN THE CELLULAR COSMOS

*A
research
warrior takes
a unique approach to
probing ALS and finds new
paths to pursue.*

—Margy Rockwood

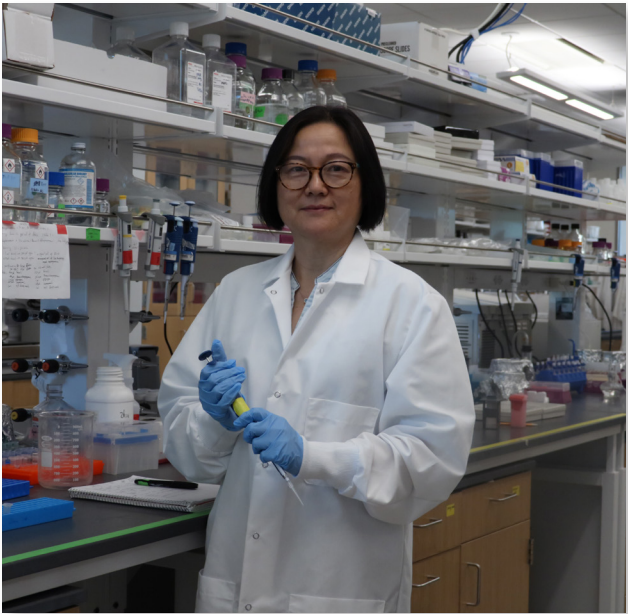


People like to stargaze, but even so, we can feel overwhelmed by the unfathomable quantity of celestial bodies and the distances that stretch beyond our visibility. Through history, we have corralled facts and figures to try to solve the mysteries of the universe, but a bit of stargazing can be a sobering reminder that despite our best efforts, there is still so much to uncover. The very best minds have failed in this.

Likewise, in our drive to find the causes of devastating diseases like amyotrophic lateral sclerosis (ALS), the innumerable factors to explore can be daunting. We are reminded that there is a vast kind of inverted cosmos within each living body.

"If you dive inside a small cell, there is infinity, a seemingly endless universe of bodies and movement going on," says Jingsong Zhou, professor of kinesiology and the associate director for the Bone-Muscle Research Center at The University of Texas at Arlington.

This challenge notwithstanding, Dr. Zhou wades through the cellular universe to learn when, how, why, and where the neuromotor transmission we depend on for every movement goes off-course in ALS. Her passion and ongoing



Dr. Jingsong Zhou

work toward this end and her seminal discovery of a mitochondrial defect in ALS skeletal muscle cells, have heightened hopes for shortening the timeline to interventions.

FROM CLINIC TO BENCH

ALS, also known as Lou Gehrig's Disease, is a fatal disease characterized by progressive motor neuron death and severe muscle wasting. Only 10% of cases are linked to heredity, making the search for relevant culprits even more challenging. For the past six years, Zhou's lab has enriched UTA's program for pursuing this mission, more than doubling the grant resources available to support this work.

"ALS is indeed a devastating disease, and Dr. Zhou's work has made substantial contributions to a better understanding of the disease and potential underlying mechanisms" says Paul J. Fadel, director of clinical translational science in the College of Nursing and Health Innovation. "She is emerging as a prominent leader in this important area of research."

"As a child, I was interested in how the human body works and why diseases occur, which is what led me to Medical School" Zhou says. "But I have always been driven to ask questions and try to find solutions, so I decided to pursue medical research instead of clinic practice."

"Fortunately, I was accepted as a Ph.D. student by Rush University in Chicago to study molecular biophysics and physiology under the guidance of Eduardo Rios, where I have developed my quantitative thinking skills and gained fundamental knowledge in muscle physiology."

After doing her postdoc work at Vanderbilt University in cardiovascular research under the guidance of Katherine Murray, she then returned to Rush as an assistant professor of molecular biophysics and physiology. Zhou gives special thanks to Robert Eisenberg, the department chair, and Eduardo Rios for giving her the opportunity to continue pursuing her original interests in muscle physiology.

FRUITS OF THE SKELETAL MUSCLE BIAS

Zhou has been studying skeletal muscle for the better part of her 30 years in research. Her ALS studies originated in 2006 when Han-Xiang Deng at Northwestern University offered her an opportunity to use the first rodent model of ALS.

"We isolated individual skeletal muscle cells from ALS mice and examined them under a confocal microscope. The first stunning finding was that the live ALS muscle cells showed defective mitochondria right at the site of the neuromuscular junction," Zhou says. This was the first time, to her knowledge, that the mitochondrial defect had been visualized in live ALS muscle cells under a confocal microscope.

Due to large energy demands, muscle cells are packed with mitochondria, the "powerhouse of the cell." They are the engine that drives movement and also decides each cell's fate. The neuromuscular junction is the site of two-way communication between muscle cells and motor neurons, controlling muscle contraction.

"The new discovery made us ask why this type of mitochondrial defect occurred at the site of neuromuscular junction, what would be the consequences of this defect, and could this be a therapeutic target to alleviate ALS disease progress," she says.

With this evidence, Zhou obtained her first

ALS research grant from the Muscular Dystrophy Association (MDA) in 2007 and published her first paper on ALS in 2010 (Since then, she has been on track to dive deeper into the role of muscle during ALS pathogenesis by looking at mitochondria, calcium signaling, and other cellular processes that are critical to muscle contraction.

Zhou says her finding was possible because she works counter to the tide in ALS research.

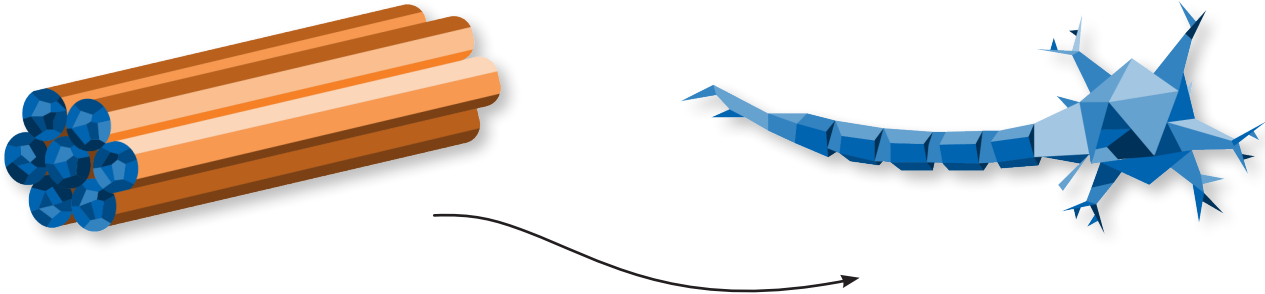
"The mainstream approach is to start with the neuron and work toward the muscle cell," she says. "But we decided, since the muscle is where the problem manifests, we should go backward from the muscle back to neurons."

REPAIR MECHANISMS PROBED

The studies of Zhou's research team on mitochondrial defects in ALS skeletal muscle uncovered a pathological event that was not identified before. They found that the surface membrane of muscle cells is fragile in ALS, even at the early stage of the disease. The cell membrane integrity can't be maintained, especially at the site of neuromuscular junction.

"Muscle membranes experience constant physical damage due to contraction and relaxation movements," Zhou says. "But our muscle cells have mechanisms for repair. What we have found is that one specific muscle protein (named MG53) lost its membrane repair function

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Skeletal muscle cell

Neuron

in ALS muscle."

Through a collaborative study with Jianjie Ma at the University of Virginia and Lyle Ostrow at Temple University, the team found that the synthesized MG53 protein could delay ALS disease progression when applied through intravenous infusion in the tested ALS mouse model (<https://doi.org/10.3390/antiox10101522>). This line of study has been supported by the Department of Defense (DOD) and the National Institutes of Health (NIH).

TREATMENT HOPES

The path to a full understanding of ALS is confounded by the sheer magnitude of molecular life and activities that take place in that inverted cosmos within. For this reason, a one-factor "Eureka" discovery is unlikely to be in store.

Zhou may have found the mitochondrial defect in ALS skeletal muscle, but the etiology of that defect is multifactorial. Most likely, the pathophysiology involves epigenetics, meaning it is related to many molecular signals that turn certain gene expressions on and off.

Currently, there are three FDA-approved ALS drugs on the market, which focus on quelling toxic neural excitability and reducing oxidative stress. However, the field still demands for more effective treatments to extend patients' life span and improve life quality.

"We hope a cocktail designed can improve mitochondrial function, while also working as a bandage to repair the damaged surface membrane of the muscle cells, thus delaying disease progression," Zhou says.

ABUNDANT RESEARCH SUPPORT

Zhou has been serving as the principal investor or co-principal investigator on projects supported by multiple major federal grants. Four of these directly focus on ALS from NIH and DOD. The others focus on cardiovascular function and skeletal muscle aging. The most recent one is a 5-year, \$3.16 million grant from the NIH to support a collaboration between The University of Texas at Arlington, the University of Virginia, and Temple University to explore

molecular mechanisms underlying neuromuscular degeneration in ALS and toward developing potential therapeutic interventions.

"In a patient with ALS, muscles fail systemically, except for eye muscles. People with advanced ALS can still move their eyes," Zhou says. "So, we have been checking the gene expression pattern on stem cells, and have found differences between eye muscles and somatic muscles. This raises the hope of whether we can find a way to recreate the targeted molecules found in eye muscle cells to make ALS patients' somatic muscle cells work better."

Her work over the years has been supported by partners at the NIH, the Muscular Dystrophy Association, the DOD, the ALS Association "Ice Bucket Challenge," and the Bank of America Victor E. Speas Foundation. Generous support has also come from other organizations in Texas communities.

"We share a sense that this quest is bigger than us."
— Dr. Jingsong Zhou

BIGGER THAN US

Zhou says that as potential targets and treatments come to light, there is a five-level process that follows.

"In the lab, we try to understand the disease first at the gene, cellular, organ, and the animal model level – which is where my lab works, and then at the level of human studies," she says. "We hope we can find potential molecular targets that can be tested at all five levels through collaboration among labs."

When she left Rush, and later Kansas City University, she says she had the collegial support and blessing of the leadership there.

"They knew I was going somewhere where I had greater resources, and the moves were with

their blessing and support," Zhou says. "We share a sense that this quest is bigger than us."

Sharing the same research interests and passion of Dr. Marco Brotto, the director of the Bone-Muscle Research Center, Zhou happily joined the center and the Department of Kinesiology in 2018.

"Together with faculty members in the Center, we made an effort to build up a multi-omics research platform that not only supports the researchers in our center, but also colleagues outside the center," she says.

"Dr. Zhou's research has been instrumental in the development and growth of the Bone-Muscle Research Center, for which she serves as co-director," says Dr. Fadel. "Her research efforts and tremendous contributions are putting the College of Nursing and Health Innovation and UT Arlington in the spotlight for advancing ALS related research."

Zhou credits her research team for success in meeting the challenges each project presents.

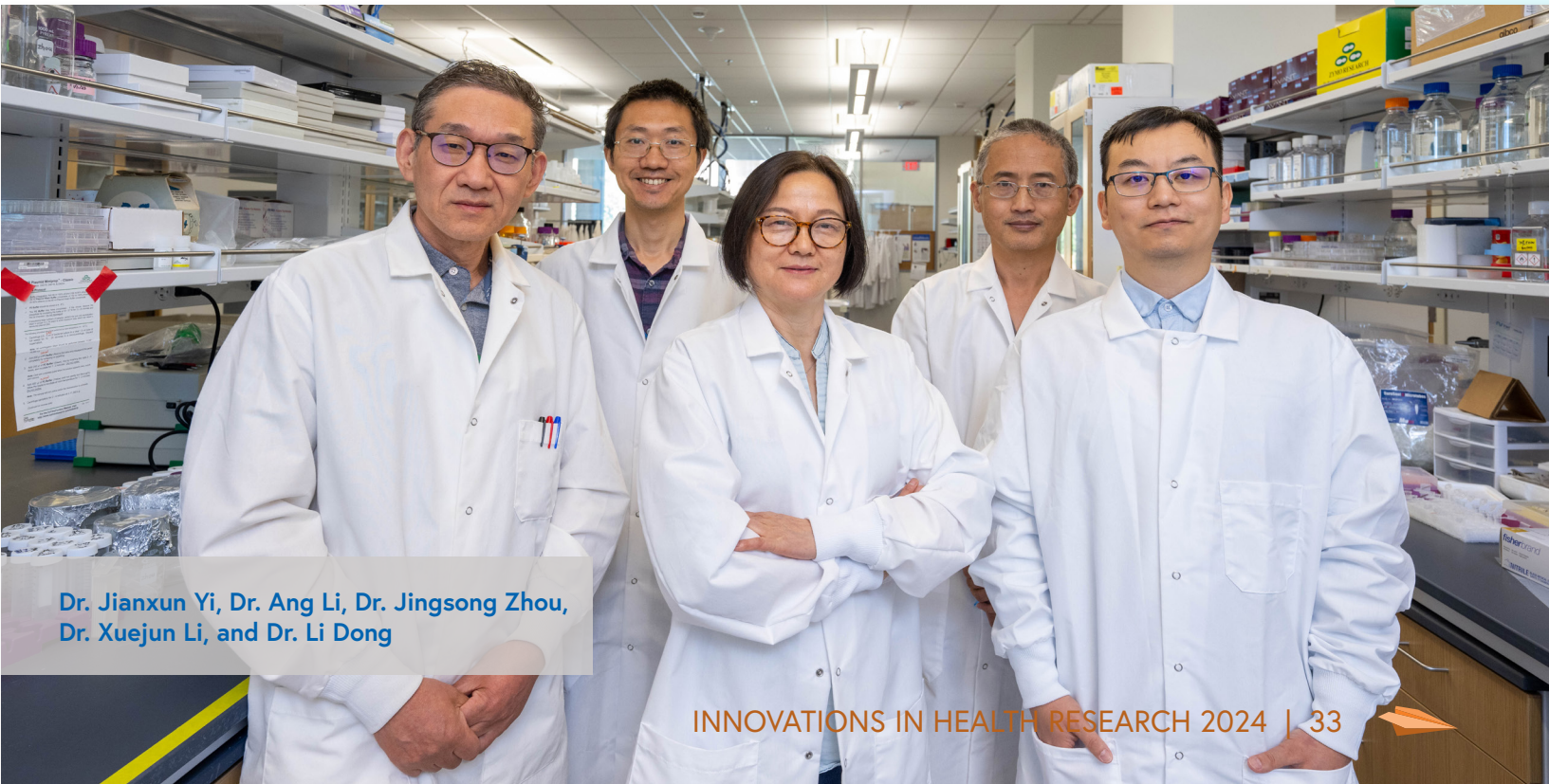
She says, "I really use my heart to build the team and find people who share the same passion. Most importantly, I respect them—we respect each other as scientists. A research project will not succeed from a single person's effort. We work together as a unit and help each

other out. The same is true with my colleagues at other institutions."

"Of course, nothing happens without the support of the leadership and the administrative staff from the department, college, and University, although their names never appeared on our publications. In the past six years, my research team received numerous supports. To name a few, the department purchasing/ accounting support, animal facility, biosafety, grant management support, and more. Without their support, it would not be possible to rebuild a fully functional research lab at UTA."

Discovery, whether of human cellular architecture or the stars, takes extraordinary curiosity, patience, and a willingness to be a building block in a structure that may not yet be fully conceivable. In a world where researchers must scramble toward grant deadlines and publish or perish, Zhou's words are a heartening reminder of a medical professional's original inspiration.

"I would not do something that didn't match up with my passions," she says. "I have medical training, and I see patients suffering. I wish that I can do something to help patients, by understanding the diseases and finding treatments." ➡



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