The Man Behind A Biological Blockbuster

WORDS BY MARYANN BRINLEY / PHOTOGRAPH BY ANDREW HANENBERG

Jianjie Ma, PhD, has discovered the "pixie dust", a gene named MG53 that can preserve life. The discovery of MG53 responsible for repair and regeneration of cell membrane damage throughout the body is nothing short of miraculous. "We have a molecule that can potentially lead us to a better and healthier life," explains the soft-spoken, yet dynamic researcher who has been a University Professor in the UMDNJ-Robert Wood Johnson Medical School's Department of Physiology and Biophysics for the past decade.

For centuries, scientists have surmised that when a cell is damaged, there must be a sensor or a gene which alerts the mechanism inside, telling where the injury occurred and coordinating the action to make the repairs. "This is something our bodies have, in every cells and tissues, but what was it?" When defective, in patients with muscular dystrophy, for instance, the repair work can't take place and we lose muscle strength. The heart has the same problem in disease, when stress exceeds the repair capacity heart will stop beating. The same is true for our skin, when constant exposure to sun light and environmental hazards cause damage to our skin lining cells and lead to wrinkle in our face. In aging, , the repair capacity of our body may decrease, which lead to loss of memory and loss of strength.

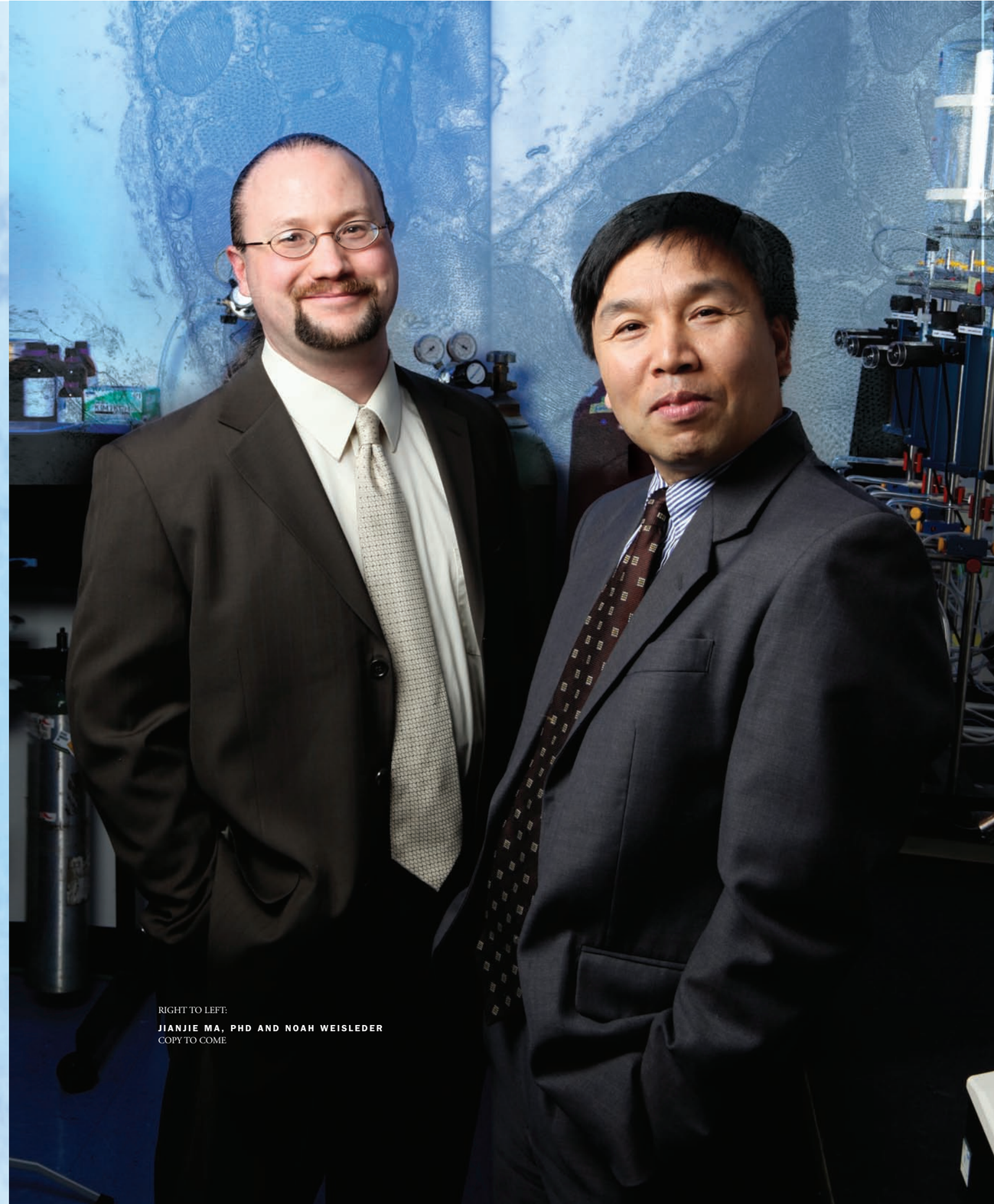
Ma pulls out his laptop. "Let me show you how MG53 performs its magic function of cell membrane repair" he says. On the screen, a needle is shown to penetrate into a cell grown in a culture dish. Within a few seconds following the injury, a massive migration of MG53 molecules is observed at the needle-injury site to plug the hole in the cell . Even cutting the cell completely in half can't kill it when MG53 proteins are present. In this situation, a seal is formed along the cut edges almost instantaneously to allow the broken cell to survive. Yet, in a third screen, the needle goes into a muscle cell in which the gene for making MG53 has been knocked out. Then, the cell quickly shreds apart right on screen, dying before our eyes.

Like that sprinkling of pixie dust, MG53 holds the power of regeneration in real human life. This surprising and unexpected discovery is a stunning scientific achievement that could soon have a profound impact on wound healing, surgical trauma, geriatric medicine, cardiovascular disease, sports medicine, neurodegeneration, just to name a few. Perhaps, a few years from now, we will see a UMDNJ-derived pill that can cure or prevent damage to our muscle and heart, protect our skin from developing wrinkles, or allow us to live a younger and healthier life.

Dr. Ma is married to his high school sweetheart from China, Junxia Xie, a former UMDNJ researcher now working for a pharmaceutical company. His wife's essential wisdom has often proved key to his success. She helps him focus, he says. "Women just think differently from men." Ma also credits his father, Futang Ma, and mother, Liuju Han, neither of whom are scientists, for encouraging him to take advantage of opportunities. Right after graduation from Wuhan University in China in 1983, Ma was chosen as one of the top 100 physics students in China to study in the US sponsored by Professor T.D. Lee (a Nobel laureate in Physics at Columbia University). He earned his PhD at Baylor College of Medicine and arrived at UMDNJ in 2001, as the first group of university named professors, where he founded the Graduate Program in Physiology and Integrative Biology as a joint program with Rutgers University. He is currently the Acting Chair of Physiology and Biophysics at UMDNJ. He also keeps a close tie with China, and several times a year, he would return to China to teach a graduate course and to perform collaborative studies.

"Science is a demanding hobby," Ma admits, "family and friendship are the main driving force behind. My children and students are what motivate me every day." Photos line the windowsills and desk of this father of three and consummate mentor of young scientists. Dr. Ma mentioned that Dr. Noah Weisleder (the smiling person present in the photo), a key member of his research team and an Assistant Professor at UMDNJ , played a very important role in the discovery of the MG53 gene and their ongoing developmental effort toward translating their laboratory discovery into therapeutic applications.

Like the Peter Pan who needed pixie dust and a happy thought in order to soar, Ma believes, "Joy opens the mind. Some of our findings may inspire others, but will soon be forgotten.." And Ma wields this light, almost magical touch everywhere in life. When asked to point to his proudest professional accomplishment, he quickly counters, "It is my students who actually did all the work. Seeing their smiling face will always be my joy". ■



RIGHT TO LEFT:

JIANJIE MA, PHD AND NOAH WEISLEDER
COPY TO COME

Discovery of Membrane Repair Gene Could Revolutionize Regenerative Medicine

BY JIANJIE MA, PHD

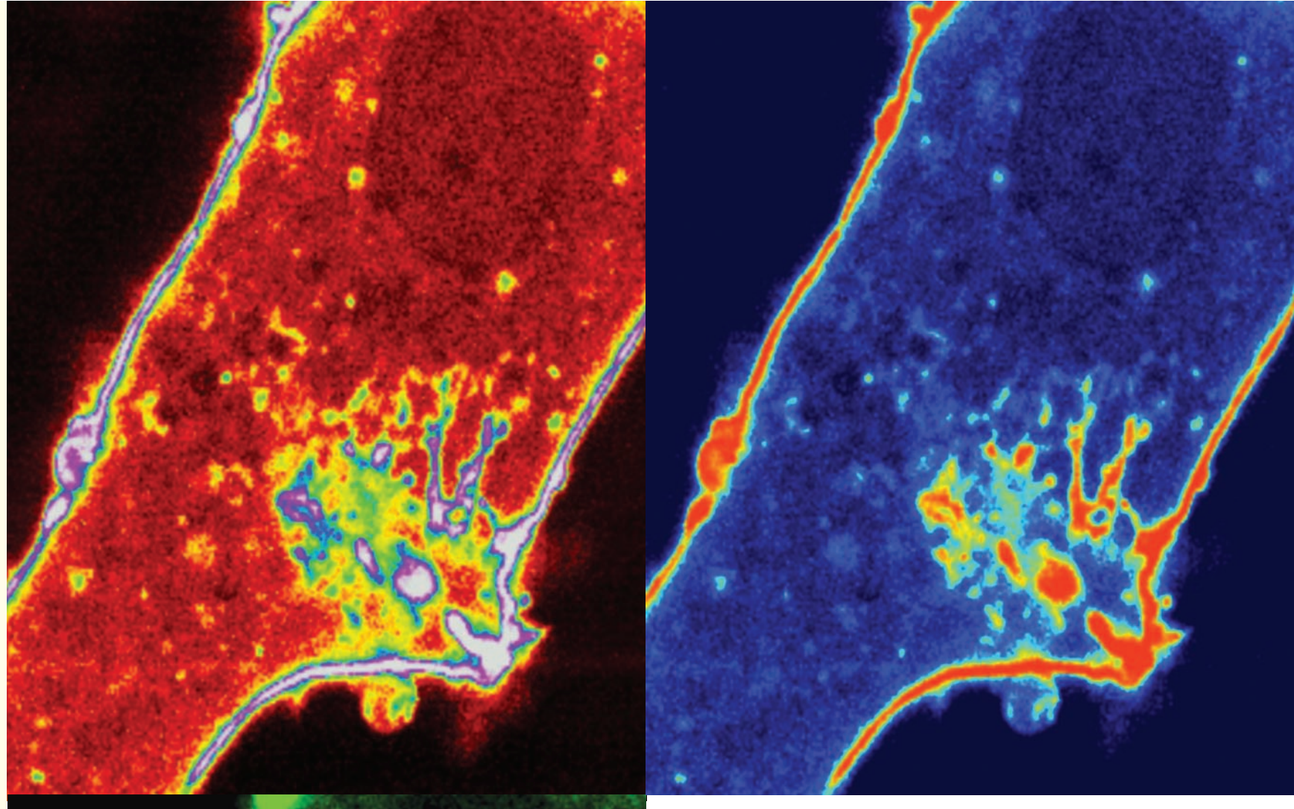
IMPORTANT SCIENTIFIC DISCOVERIES that advance the state of biomedical research depend on integrated teams of scientists with various skills who can produce a synergistic environment to foster innovative studies. Building a world class research team was one of my goals when I came to Robert Wood Johnson Medical School (RWJMS) in 2001. Part of accomplishing this goal was expanding collaborative efforts with researchers around the world. One such collaboration was with Dr. Hiroshi Takeshima at the Kyoto University who had developed a unique approach for cloning new genes from an immuno-proteomic monoclonal antibody library. While this approach led to the discovery of several novel genes, a large group effort is required to gain an understanding of how these genes contribute to physiological and pathophysiological functions. My group at RWJMS addresses this challenge through a variety of methods that run from biochemical assays to single cell experiments and into animal models. Through the use of a wide variety of models and techniques the researchers in our group are able to understand the normal physiological function of these genes and also establish how dysfunction of these genes can contribute to the progression of human disease. As would be expected, this integrated approach requires the efforts of many talented investigators. One key researcher in this effort is Noah Weisleder, PhD, an assistant professor at RWJMS. Dr. Weisleder was originally recruited to join my laboratory before forming his own independent research effort in recent years. Our joint research effort has led to discovery of calcium signaling abnormalities that contribute to muscular dystrophy and identified a muscle specific gene, Mitsugumin 29, as a biomarker of aging skeletal muscle that can act as a sentinel to shield skeletal muscle from age-related decrease in performance. However, one of the most exciting discoveries occurred recently as we found another gene, Mitsugumin 53 (MG53), which is an essential component of the plasma membrane repair machinery in human cells.

In a fundamental sense, the plasma membrane is the minimal unit that defines what we consider to be a cell. Maintenance of plasma membrane integrity is an essential process for nearly every cell, which helps to explain why cells evolved a highly conserved plasma membrane repair mechanism that appears in most cell types in the human body. Many previous studies indicated that repair of acute damage to the plasma membrane was an important aspect of normal cellular physiology, and disruption of this process could result in a number of different diseases, including muscular dystrophy, ischemic damage during a heart attack, pulmonary disorders and many other syndromes. However, it has been difficult to target this pathway for regenerative medicine approaches because the pathways facilitating membrane repair were poorly understood.

Studies from my laboratory identified that MG53, a muscle-specific TRIM family protein (TRIM72), is an essential component of the acute membrane repair machinery. MG53 acts as a sensor of oxidation to oligomerize and then recruit intracellular vesicles to the injury site for membrane patch formation. Further studies indicate that disruption of MG53 function results in muscular dystrophy. Additional research currently underway indicates that MG53 also plays an essential role in the heart and that disruption of MG53 can result in increased cardiac dysfunction following a heart attack. Such discoveries rewrote our understanding of cell membrane repair and have generated significant scientific interest worldwide.

These discoveries increased our understanding of the mechanisms of cell membrane repair in many different tissues. However, our research team is greatly interested in pursuing translational medicine approaches that can move such basic science discoveries from the laboratory into a clinical setting where they can benefit human patients. As part of this effort, Weisleder and colleagues found that recombinant MG53 protein could be directly applied as a therapeutic reagent for a number of different diseases, even in tissues where MG53 would not be normally expressed. Such an approach has vast potential for the treatment of many diseases where compromised membrane repair leads to pathology, both in the muscle and heart, as well as in the skin, lungs, brain and other vital organ systems.

Vince Smeraglia, Director of Patents & Licenses at the RWJMS Office of Technology Transfer and Licensing, immediately recognized the importance of this exciting discovery and RWJMS pursed international patents on this technology. Following the support and encouragement from Dean Peter Amenta, MD, Dr. Weisleder and I founded a biotechnology company, TRIM-edicine Inc, to develop MG53 and other novel genes as therapeutic agents for human diseases. TRIM-edicine has now been in operation for more than two years and has made significant progress in commercialization of MG53, including establishing joint development efforts with established partner companies. Further efforts both in academic laboratories at RWJMS and commercial efforts outside of the University will help to translate the basic science discoveries of today into the cures of tomorrow. ■



THE COVER ILLUSTRATION IS A PSEUDO-COLOR IMAGE OF A MUSCLE MYOTUBE TRANSFECTED WITH GFP-MG53. WHEN THE CELL IS INJURED, MG53 TRANSLOCATES TO THE INJURY SITE TO ASSIST IN THE FORMATION OF A MEMBRANE REPAIR PATCH TO RESEAL THE DAMAGED PLASMA MEMBRANE (LOWER RIGHT). MG53 INTERACTS WITH OTHER PROTEINS, CAVEOLIN-3 AND DYSFERLIN, TO FACILITATE THIS MEMBRANE REPAIR PROCESS.