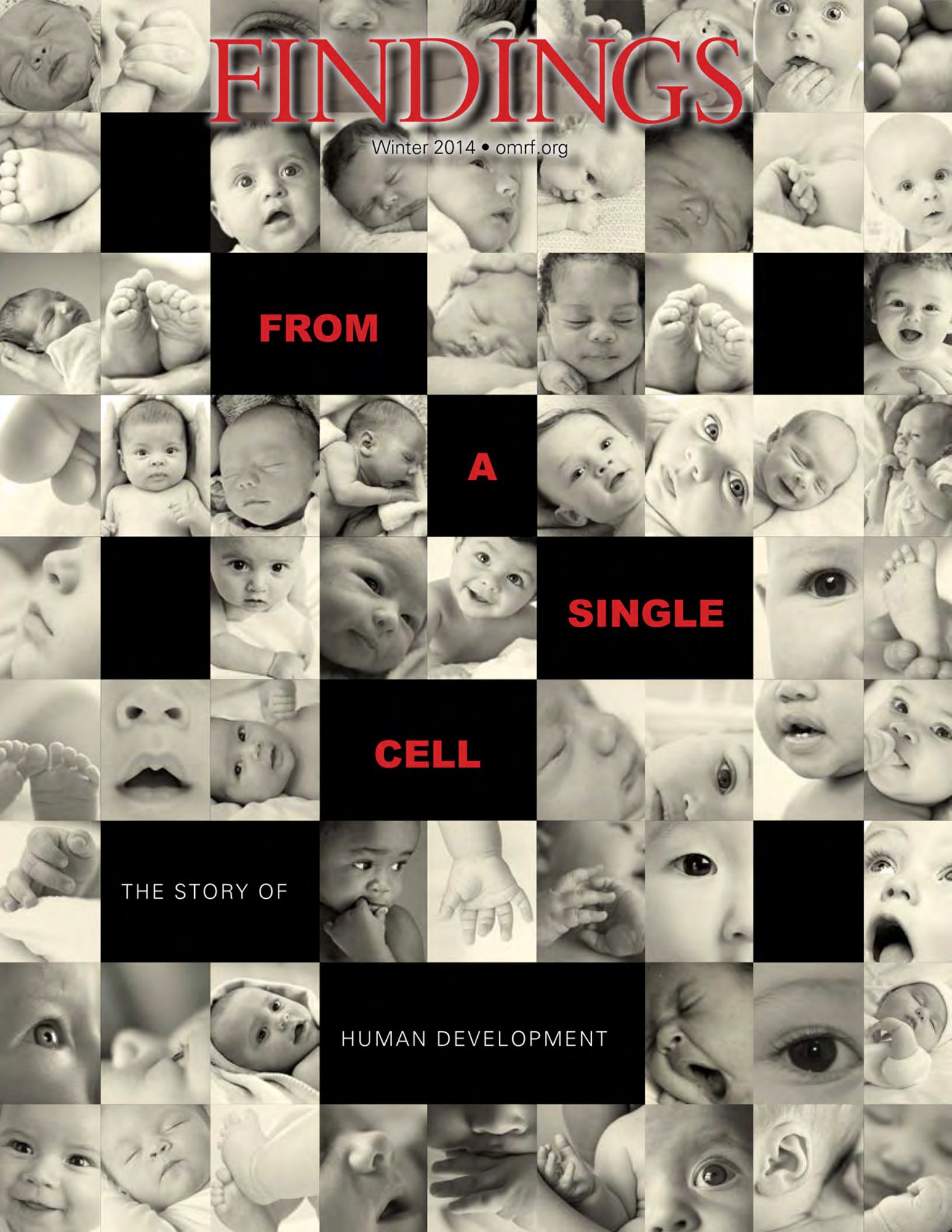
FINDINGS
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FROM
A
SINGLE
CELL
THE STORY OF
HUMAN DEVELOPMENT

WE ALL KNOW SOMEONE WHO HAS BATTLED CANCER.

The disease will steal the lives of 1 out of every 4 people. Those aren't what most of us would consider good odds. But OMRF researchers are working each day to change these numbers.

Right now, doctors are treating Oklahoma brain cancer patients with an experimental drug born in OMRF labs. And OMRF scientists are developing new approaches to treating leukemias, lymphomas, breast cancer and colon cancer.

Please help us make a difference in the lives of the people you love.

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OMRF

Chartered in 1946, OMRF is an independent, nonprofit biomedical research institute dedicated to understanding and developing more effective treatments for human disease. Its scientists focus on such critical research areas as Alzheimer's disease, cancer, lupus and cardiovascular disease.

A United Way Partner Agency

"THE ULTIMATE GOAL IS TO SAVE LIVES."

DR. STEPHEN PRESCOTT

OMRF, OU LAUNCH CANCER TRIAL

Glioblastoma
A fast-growing central nervous system tumor that forms from glial (supportive) tissue of the brain

Symptoms
Headaches, nausea, vomiting, seizures, neurological deficits

Standard treatment regimen
Surgery, radiation and chemotherapy

Life expectancy
One year with standard treatment, three months without

THIS YEAR, 23,000 AMERICANS will be diagnosed with brain and other nervous system cancers, and 14,000 will die from these forms of the disease. But a new experimental therapy developed by OMRF aims to reduce these grim statistics.

The investigational drug, OKN-007, began clinical trials at the University of Oklahoma's Peggy and Charles Stephenson Cancer Center in August. And it will be used to treat patients suffering from glioblastoma, an aggressive and deadly form of brain cancer.

In laboratory studies at OMRF, Drs. Rheal Towner and Robert Floyd administered the drug to rodents with glioblastomas. The treatments shrank the tumors and extended the animals' lives.

The initial phase of the new trial is focused on assessing the safety and dosage levels of OKN-007 in glioblastoma patients. If successful in phase 1, the trial would progress to subsequent stages to study the efficacy and safety of the investigational drug in larger patient populations.

"The current treatments for glioblastoma have substantial side effects and complications, and they don't provide ideal outcomes for patients," says OMRF President Stephen Prescott. "There is a desperate need for more effective therapies, and we're excited to see our investigational drug entering human trials."

To find out more about this clinical trial, including the eligibility criteria to participate, please call OU's Stephenson Cancer Center at 1-855-750-2273.

WALKING THE WALK
(AND RUNNING THE RUN)

OMRF goes the distance for employee wellness

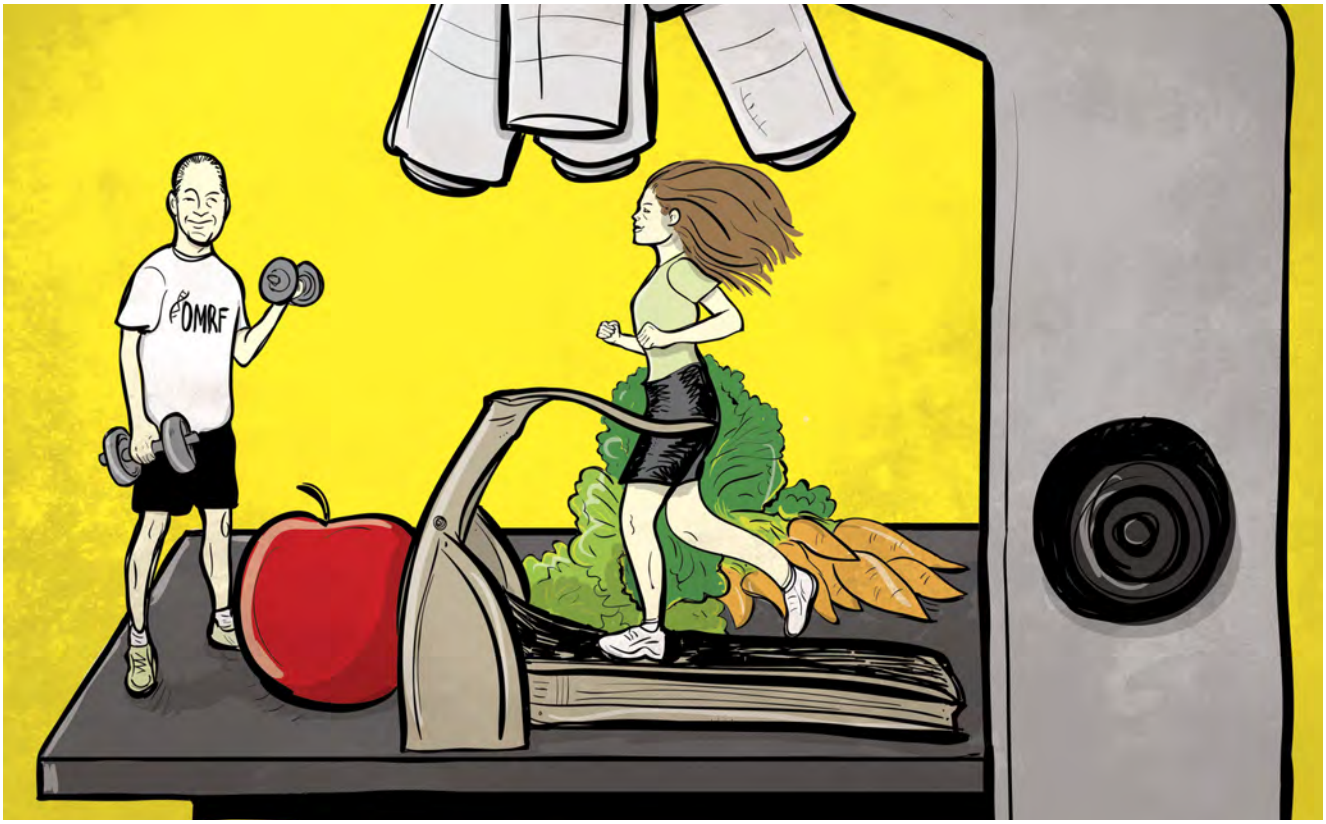
BY ADDING AN ONSITE FITNESS FACILITY, health savings accounts, an ongoing lunch-and-learn seminar series and regular fitness challenges, OMRF has built its employee wellness programs in recent years. These initiatives are a key reason OMRF has been able to keep health-care costs flat for three years running—savings the foundation has been able to pass on to employees by keeping health insurance premiums unchanged in a time of skyrocketing rates elsewhere.

This past summer, OMRF added to these efforts with an expanded menu of subsidized "green" items in its cafeteria and new healthier vending machines stocked with offerings like dried fruit and bottled water. Free biometric screenings offered OMRF staffers a quick snapshot of their health through measures like cholesterol, blood pressure and body mass index. And a new online fitness portal, LifeLab, gives employees a tool to track daily exercise, diet and other wellness activities. It also allows them to earn points toward an annual cash bonus.

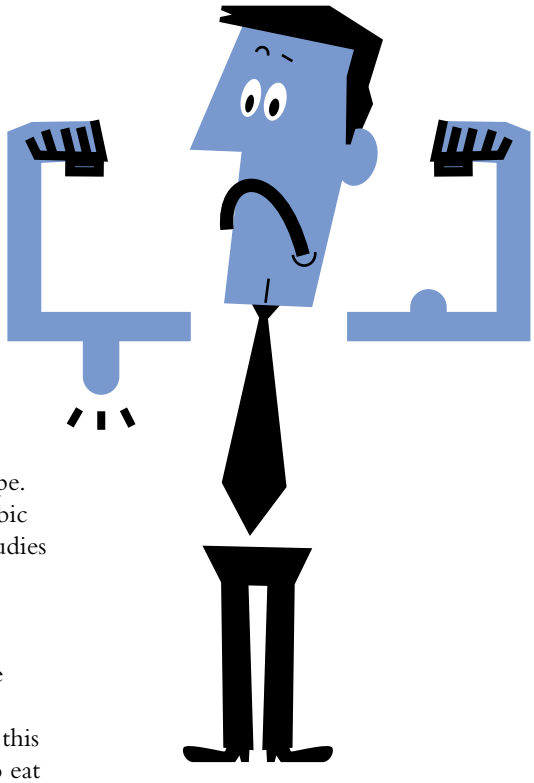
"It sounds kind of crazy, paying people to exercise and eat right," says Courtney Stevens, OMRF's vice president for human resources. "But by investing in our employees' health, we reduce sick days, boost productivity and keep our insurance premiums low." Plus, for an institution like OMRF, says Stevens, wellness just makes sense. "OMRF's mission is to help people live longer, healthier lives. We wouldn't be walking the walk unless we made that same commitment to our employees."

Nearly 9 in 10 employers now offer wellness incentives or financial rewards to employees who work toward getting healthier. That's up from 57 percent in 2009.

Source: National Business Group on Health/Fidelity Investments 2013 survey



WHEN THIN DOESN'T WIN



How can thin people develop type 2 diabetes, especially if they eat well?

- JILL HOLMES CRAIGHEAD

Although we may think of type 2 diabetes as an obesity-related illness, about 15 percent of the 26 million Americans diagnosed with the disease aren't overweight. Many of these folks fall into a category first identified by medical researchers in the early 1980s: "metabolically obese normal weight." I've also heard them referred to as TOFI—thin outside, fat inside.

The defining characteristic of TOFIs is a body that falls in the normal weight range but nevertheless displays metabolic abnormalities typically associated with obesity. These are factors like high rates of insulin resistance and triglycerides. TOFIs also tend to carry fat around the middle, which typically affects the heart and liver more than fat in the hips and thighs.

Genetics almost certainly play a role in this phenomenon, but another important factor is fitness. While most research lumps fitness and fatness together, those studies that have differentiated between the two have found that it's healthier to be fat and fit than thin and out of shape. For example, even where regular aerobic exercise doesn't lead to weight loss, studies have shown that it reduces fat in the liver, where it may do the most metabolic damage.

You can never completely eliminate your risk of type 2 diabetes. Still, to minimize your chances of developing this disease (and others), it's not enough to eat right and watch your weight. You need to stay active, too.

What are the odds of children having multiple sclerosis if they have a parent who has MS? And at what age is it appropriate to have them tested?

-DEBI CAMP

For this question, we brought in another Dr. P—Dr. Gabriel Pardo, director of OMRF's Multiple Sclerosis Center of Excellence.

Let's start by saying that the odds are very low. MS is not an inherited disorder in the classic sense, meaning that we cannot calculate the specific probability of a child having the disease if one or both of the parents have it. Nonetheless, we know that certain genes increase the susceptibility of developing MS, and we do get our genes from our parents. So how does it work?

We believe that several genes contribute to the overall risk of having MS. But other factors such as exposure to viral infections, vitamin D levels, geographical region, gender and ethnicity also come into play. Because we can't quantify or predict all those elements, we can't accurately estimate the risk of developing MS in a given individual. However, from studying large populations we have learned that if you have a first-degree relative (a parent or sibling) with MS, your risk of developing the disease is low—around 1 in 40.

What's more, there currently is no definite test to diagnose MS. So diagnosis is a complicated process based on historical evidence, abnormalities on physical examination, the results of ancillary tests such as MRI and, on occasion, a spinal fluid analysis.

The bottom line: We don't recommend specific screening in children who have a parent with MS, unless, of course, children are starting to exhibit symptoms of the disease.

SNUGGLE UP WITH A GOOD SCIENCE BOOK

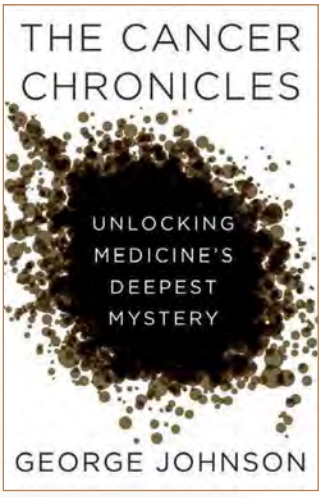
The Cancer Chronicles

Unlocking Medicine's Deepest Mystery

284 pages

By George Johnson

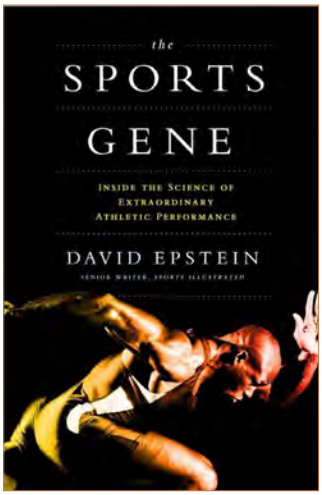
"The Cancer Chronicles" joins a pack of recent excellent books on cancer—"The Emperor of All Maladies," by Siddhartha Mukherjee; "The Philadelphia Chromosome," by Jessica Wapner; and "The Truth in Small Doses," by Clifton Leaf. But, as David Quammen wrote in *The New York Times Book Review,* this new book by George Johnson, "stands out as especially illuminating, forceful and, in its own quiet way, profound."



Johnson writes from two perspectives: as a reporter explaining what cancer is and how it occurs, and as the husband of someone struck by uterine cancer. The scientific story he tells is—no small feat—comprehensible and illuminating. But the beating heart of this book is his personal narrative, which serves as a sad reminder of the deeply human toll exacted by a disease that will touch almost all of our lives.

The Sports Gene

Inside the Science of Extraordinary Athletic Performance



352 pages

By David Epstein

As a collegiate runner, David Epstein often tested himself against his training partner. Epstein was a walk-on "who squeezed drops of improvement out of a talent-dry rock of a body." Meanwhile, his partner, the son of two former track stars, cruised through practices with apparent ease. "I just had to be tougher than him," Epstein told himself, "because I didn't have the talent."

But what really set the two athletes apart? Did one possess a genetic pre-disposition for speed? Could the other's dogged work ethic trump his seeming lack of innate ability?

These are some of the questions Epstein, a *Sports Illustrated* writer, takes on in "The Sports Gene." From DNA studies of Jamaican sprinters to testing the hand-eye coordination of Los Angeles Angels' slugger Albert Pujols, Epstein traces how far science has (and hasn't) come in solving the athletic riddle of nature versus nurture. And in spite of the title, this engaging narrative shows why neither genes nor grit alone will take home the laurel wreath.

RESEARCH ROUND-UP

Targeting Cancer

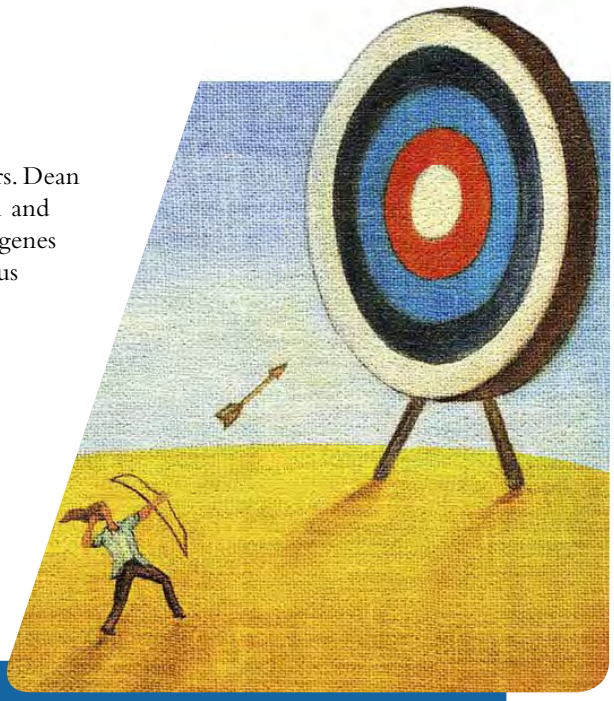
IN A PAPER PUBLISHED IN THE JOURNAL *SCIENCE*, OMRF's Drs. Dean Dawson and Regis Meyer have revealed how two genes—known as IPL1 and MPS1—are integral to the correct division of cells and life itself. If these genes can be controlled, it could help physicians target and destroy pre-cancerous cells or prevent birth defects.

In the laboratory, the researchers used high-powered microscopes to observe the process of cell division in yeast cells. But as they watched, Meyer and Dawson observed something unexpected: The cells made a lot of mistakes.

"About 80 percent of the time, the cell would begin pulling both copies off to the same side instead of pulling one towards each new daughter cell," Dawson says. "If the cell divided like that, you'd have all sorts of problems. Inappropriate chromosome numbers is a leading cause of birth defects and is a common feature of tumor cells."

With further study, the scientists discovered that the IPL1 and MPS1 genes act as quality controllers. When a chromosome gets pulled to the wrong side, the two genes correct the problem. "These genes are master regulators. If they're removed, the entire process goes haywire," Dawson says.

Several groups are now investigating ways to target IPL1 and MPS1 as potential anti-cancer treatments. According to Dawson, the OMRF research will boost those efforts. "When you understand exactly how the process works, you know how to better craft a treatment," he says.



"WE THINK THIS RESEARCH IS GOING TO BE USEFUL IN DESIGNING ANTI-CANCER COMPOUNDS."

Dr. Dean Dawson

THE PRICE OF FATTY FOODS

WHEN OMRF SCIENTISTS STUDIED THE HEART CELLS of mice that ate a high-fat diet, they discovered something counterintuitive. "We found a reaction similar to what happens with starvation," says Dr. Mike Kinter, who worked with Drs. Luke Szweda and Paul Rindler on the study. "In a sense, it tricks the cells into burning fat instead of glucose." While that may sound like a good thing, it's not. Over time, the resulting build-up of excess sugar in the bloodstream can lead to type 2 diabetes, nerve damage, kidney and eye problems, heart disease and stroke.

The research, which appears in *The Journal of Biological Chemistry,* gives scientists insight into why cells begin burning fat instead of glucose. "Our bodies just haven't evolved to deal with the modern problems of too much food and not enough exercise," says Szweda. Follow-up studies will look at the related issue of insulin dependency and could give researchers clues on how to reverse type 2 diabetes.

New Life for Old Cells

WHEN PEOPLE AGE, SO DO THEIR CELLS. This process takes a particular toll on stem cells, which play a key role in fighting infections. "As stem cells grow older, their ability to make lymphocytes is diminished," says OMRF's Dr. Paul Kincade. "That compromises the body's ability to fight infections and could explain why older patients have so much more trouble fighting even common illnesses."

In collaboration with researchers at the Osaka University Graduate School of Medicine in Japan, Kincade helped stimulate the stem cells of laboratory mice to make more of a protein known as Satb1. The result: The animals' stem cells regained much of their ability to create lymphocytes.

Published in the journal *Immunity*, the new findings might help replenish stem cells as people grow older and aid in reducing age-related illness from infections. "At least in mice," says Kincade, "this looks like a fountain of youth for the immune system."

What's a stem cell?

A "blank" or undifferentiated cell found in the human body that has the ability to create or become many different types of cells

PLATELET POWER

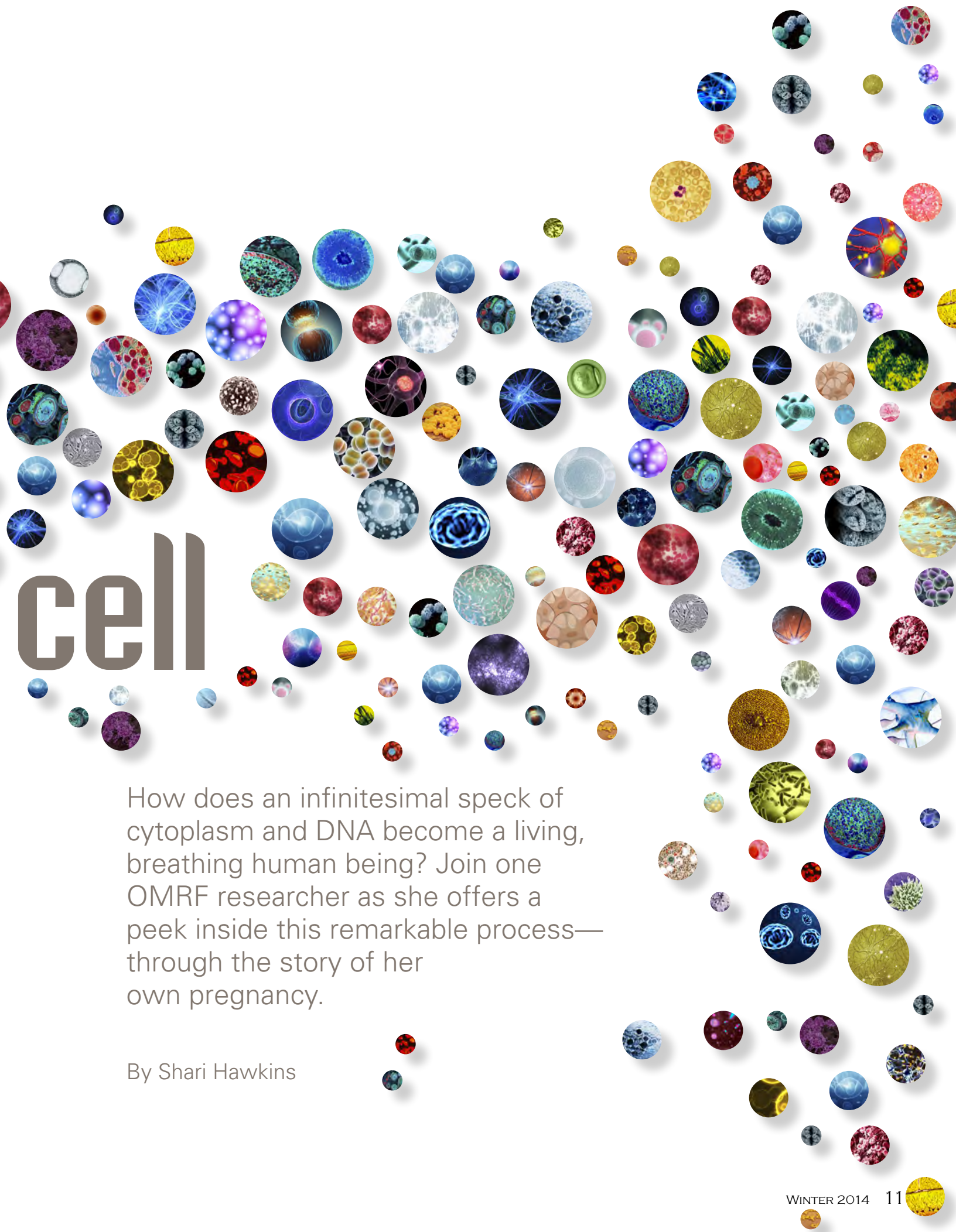
ONE WAY THE IMMUNE SYSTEM KEEPS A BODY healthy is through immune surveillance. Lymphocytes, a type of white blood cell, constantly exit the bloodstream and "check in" at the lymph nodes to learn about possible pathogens or abnormal cell growth. The function prepares the immune system to fight infections and dispose of pre-cancerous cells.

For years, scientists have wondered how lymphocytes exit the bloodstream at a large volume without causing bleeding. A team of OMRF researchers led by Dr. Lijun Xia found that platelets, which normally stop blood loss by clumping and forming plugs in blood vessel holes after injuries, activate a screening process. This process allows lymphocytes to exit into lymph nodes without letting red blood cells leave the blood vessel.

Drs. Xia, Jianxin Fu and Brett Herzog detailed the research in the journal *Nature*. The findings could alter the ways doctors use platelets to treat traumatic injuries and serious infections.

"This is a prime example of the important research that the Institutional Development Award program makes possible," says Dr. María Teresa Canto of the National Institutes of Health, which provided funding for the research. "Dr. Xia's study sheds light on a process that is key to vascular health as well as to the development of inflammation and associated diseases."

From a single



cell

How does an infinitesimal speck of cytoplasm and DNA become a living, breathing human being? Join one OMRF researcher as she offers a peek inside this remarkable process—through the story of her own pregnancy.

By Shari Hawkins

The sound of the surf lingered in her mind. Pushing open her front door, Courtney Griffin could still feel the sand between her toes. The young cardiovascular biologist had spent the last week at the beach with her scientist husband, Tim, enjoying a respite from the long hours they each worked as post-doctoral fellows in research laboratories—she at the University of North Carolina and he at Duke University.

But Courtney hadn't made it more than a few steps into her home before she saw the message light on the phone blinking. *I hope it's not the lab*, she thought as she pushed play.

This is Dr. Schlegel's office. The results of your triple-screen test are in. We'd like to schedule an ultrasound as soon as possible. Please call our office to make an appointment.

Beep. Memories of the past few lazy days at the beach vanished as Courtney reached to replay the recording. She looked down and put a hand on her growing baby bump. *You're still moving around*, she silently told the little person in her belly who seemed to grow more restless and active with each passing day.

The first 18 weeks had sailed along without any major issues, and now—what? She didn't feel any different. But the message had mentioned her triple-screen test. This routine screening procedure measures a protein present in neural tube defects or Down syndrome. She knew that an unfavorable result could mean devastating news. *Whoa, whoa, whoa*, she thought. *Don't get ahead of yourself. This is just a preliminary result that doesn't mean anything by itself. The ultrasound will tell us the real story.*

Before the ultrasound, Courtney and Tim met with a genetic counselor to go over the results of her triple-screen test. The pair sat nervously as the counselor went over the numbers. As a scientist working in a laboratory that studied developmental genetics—how DNA influences the process of growth—Courtney knew far more than the average person about what should and shouldn't happen during pregnancy. And when she saw the numbers from her test, she recognized that they were off the charts: triple, sometimes even quadruple, the normal levels.

These results could suggest a serious health issue, said the counselor. *Or multiples. We could be looking at triplets.*

Triplets? At once, Courtney felt both hope and a new wave of anxiety. Images of three cribs, hundreds of bottles and thousands of diapers swirled in her head. Braces in triplicate. A trio of surly teenagers. Triple tuition costs.

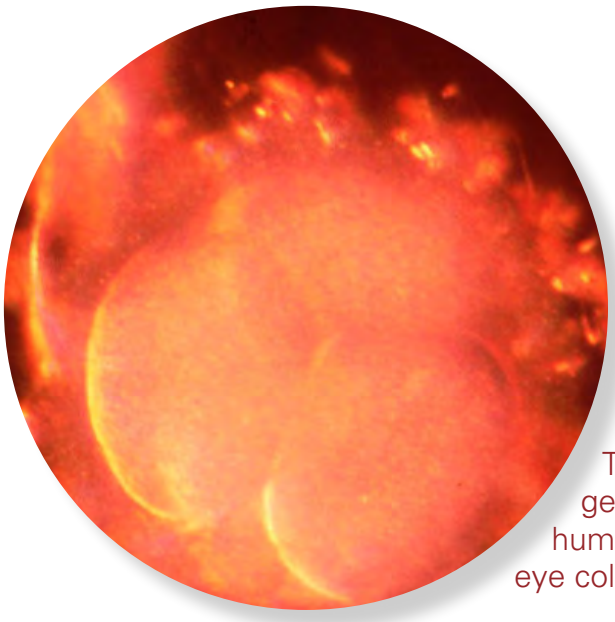
Dr. Courtney Griffin knew that her results from a routine 18-week pregnancy screening test were anything but routine.

Far worse than the potential financial burden, though, was the thought that their little one—or ones—might have serious health issues. *But how could it be?* Courtney wondered. *I've done everything right. I eat healthy food. I always take my prenatal vitamins.*

Her mind raced as the ultrasound tech set up the equipment. Courtney stared at the ceiling, gripping Tim's hand. The chill of the gel on her stomach got her attention. While the technician guided the sensor back and forth across her belly, Courtney tried to make sense of the grainy images on the gray screen in front of her.

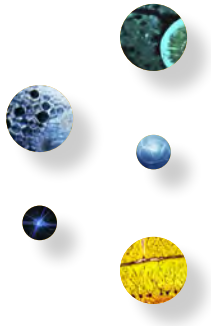
In a moment, the reassuring whoosh, whoosh, whoosh of amplified fetal heartbeats echoed through the room. *Everything looks good,* said the technician. *Normal.* Never had such a seemingly mundane word meant so much to the couple. Then the technician began to count. *One. Two. Two!*

The genetic counselor's hunch had been right. Sort of. Courtney was carrying twins.



Day 1

A sperm joins with the egg to form a single microscopic cell. This one cell contains the complex genetic blueprint for every detail of human development: gender, hair and eye color, height and much, much more.



By the time Dr. Courtney Griffin learned that she would give birth to twins, thousands of crucial steps had taken place in their embryonic development. While the Griffin children had not yet grown to even an inch in length, much of who they would become over the next 80 years or so had already been mapped out. To understand why, it helps to know a little about chromosomes.

Chromosomes serve as the mechanism for passing parents' traits to their offspring. Each chromosome contains about 1,000 genes made up of strands of DNA wound tightly around proteins. The DNA serves as a sort of blueprint that holds all of our genetic information, the individual genes that determine height, eye color, gender and every other detail that makes us who we are.

Most human cells carry 46 chromosomes—23 pairs. But reproductive cells are the exception to this rule: Sperm and egg cells carry only one copy of each chromosome.

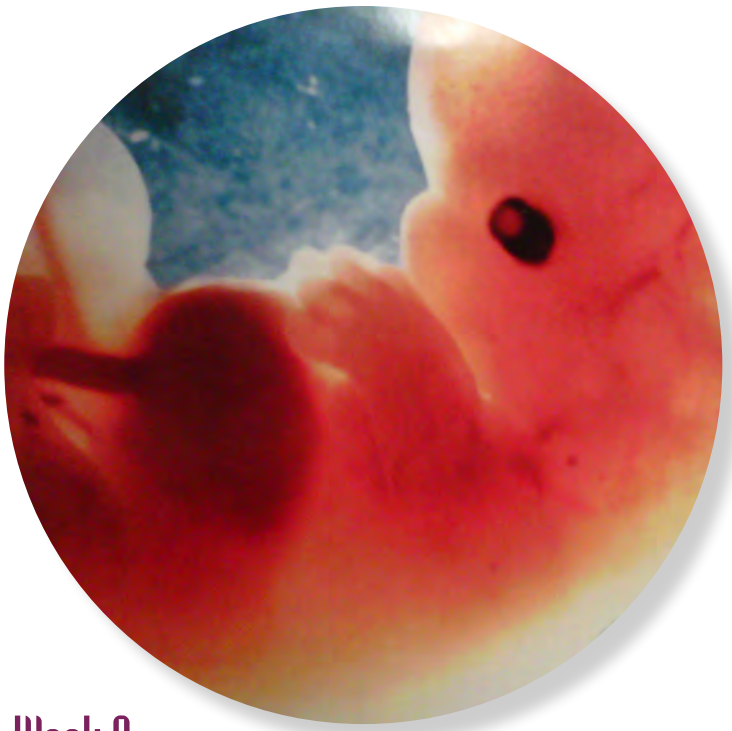
At the moment of conception, a sperm carrying 23 of the father's chromosomes joins with the mother's egg, which also contains a single copy of each of her 23 chromosomes. The sperm and egg unite to create an embryo with 46 new and unique chromosomes, each a blend of those contributed by the parents. That single cell then launches a series of divisions—a staggering trillion or more by the time the process is complete—that eventually result in a human baby.

Cell division, though, is far more complicated than simply cutting cells in half. The process begins with each of 46 chromosomes duplicating themselves, creating 46 identical pairs. Then, like soldiers standing back-to-back in formation, the 46 pairs line up, each facing the opposite direction from its twin. All the pairs must be in line, or the process halts.

Once the final pair aligns, a sort of biological knife cuts the pairs in two, and the chromosomes pull themselves to opposite sides of the cell. This split sends one complete copy of a cell's genetic information to each side. Then the cell crimps down the middle and splits. The result: Two cells, each containing exact copies of all the chromosomes that came before it. The process then repeats itself. Over and over and over.

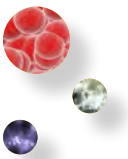
"Cell division requires intricate precision, because there are hundreds, maybe thousands, of steps to the process, and they have to occur in the proper order," says Dr. Gary Gorbsky, who heads OMRF's Cell Cycle and Cancer Biology Research Program and has spent more than three decades studying the process of cell division. "If there's even one laggard chromosome, there's a checkpoint system that stops the whole thing from going forward until that one makes it into the alignment. It's a very precise, high-fidelity system. It has to know exactly when to turn things on and off."

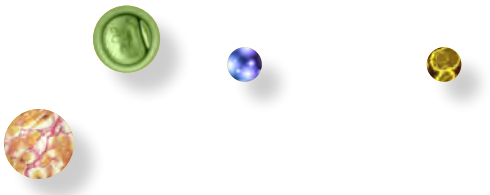
Still, with thousands of cells dividing at once, mistakes can occur. Every chromosome contains about 1,000 genes, each a sequence of deoxyribonucleic acid—DNA—that determines a particular trait. If just one of those chromosomes lines up incorrectly, says Gorbsky, "you've essentially changed the function of all 1,000 genes." These genetic mistakes may result in disease, which can be passed on to future generations.



Week 8

At a little more than an inch long, the developing life is now called a fetus. The stomach produces digestive juices, and the kidneys have begun to function. The fetus' body responds to touch, although the mother won't feel movement for weeks.





The cell division process goes awry when the embryo ends up with the wrong number of chromosomes. "A missing chromosome is the leading cause of spontaneous miscarriage," Gorbsky says. More than half of first-trimester miscarriages result from chromosomal issues in the fetus, many times before the mother is even aware of the pregnancy.

But chromosomal errors don't always result in the death of the fetus. When the embryo receives an extra copy of chromosome 21, for example, the result is Down syndrome. "There are so many ways this process can go wrong," Gorbsky says. "But that's the amazing thing about human biology: it is almost always self-correcting. Most of the time the system works exactly as it should."

Within five days of fertilization, that first single cell will have grown into a ball of about 16 undifferentiated cells. At this point, the cells are still considered "stem cells," meaning that they possess the ability to become any type of cell in the body—heart, lung, bone or anything else needed to build a human. "Cells in the very early stages of development really aren't obligated to becoming any certain sort of cell," says Dr. Lorin Olson, whose lab at OMRF focuses its research on the study of stem cells.

But as they mature, the stem cells begin emitting and receiving signals to and from other cells. How and when does this signaling start? "That's what everyone wants to know," Olson says. "We know it happens, but scientists have yet to identify the trigger that sets the process in motion."

The signals travel back and forth, cell to cell, encouraging them to migrate to specific areas of the embryo. In response, in a process known as gastrulation, the stem cells break away from their initial locations and begin grouping themselves into modules or clusters that will become various body parts. At this point, says Olson, the die is cast. "The stem cells are fully committed to becoming a certain type of cell. There's no going back."

The cells that move to the outer layer of the cell bundle, called the ectoderm, will become skin cells. Others migrate to the bundle's center, or endoderm, to form internal organs like the heart, intestines or liver. Between the two layers, cells create the mesoderm, a middle layer that becomes bone and muscle. Although the cells have now assumed a unique identity (and, thus, are no longer stem cells), division continues. Only now, the division is much more specialized, resulting in the growth of specific cell types like organs, skin and muscles.

The first major organ to form is the heart, which starts taking shape about a month into the pregnancy. "When an embryo is very tiny, all the oxygen and food can kind of diffuse in from mom," says Dr. Courtney Griffin, who joined OMRF in 2008 to study blood vessel growth as part of OMRF's Cardiovascular Biology Research Program. (She and Tim, also an OMRF scientist, are now parents to two healthy ten-year-olds, but we'll get to that soon enough.) "As the embryo grows, the diffusion of oxygen and nutrients can't get into the inner parts. That's why the heart and circulatory system have to form early, because the cells won't survive without that consistent nourishment."

The heart derives from two primitive heart tubes. The tubes fuse together, bending and twisting to form a simple version of the heart. About halfway through this process, around week 6 of the pregnancy, the heart starts to beat. At 65 contractions or so a minute, it circulates blood cells throughout the embryo, which is not yet as big as a grain of rice.

Over the next six weeks, the remainder of the first trimester of pregnancy, the fetus (as it becomes known at week 8) will grow at an astronomical rate. It will stretch from less than a quarter-inch to four inches long. All of its major organs and body systems will fully form, as will its arms, hands, fingers, feet and toes.

"With all of the growth and development taking place, fetuses are at their most vulnerable during the first trimester," says Dr. Stephen Prescott, a vascular biologist and OMRF's president. During this crucial phase of pregnancy, Prescott says, a mother needs to be particularly vigilant about protecting the child growing inside them. "Especially at this stage, exposure to drugs, alcohol, tobacco, radiation, certain toxic substances or even viruses like German measles can cause major damage and birth defects."

Still, the end of this phase signals an important milestone. "Because a baby's most critical development has taken place," says Prescott, "the chance of miscarriage drops considerably after the first trimester."

Week 16

About the size of an avocado, the fetus now sleeps, awakens and exercises its muscles energetically. The fetus turns its head, curls its toes, and opens and closes its mouth. Breathing amniotic fluid helps develop the respiratory system.

Week 32

What started as a single cell now has toenails, fingernails and hair and the skin is becoming soft and smooth. It's getting crowded in there as the baby, now more than a foot long, plumps up in preparation for birth.

Courtney Griffin peered at the ultrasound screen, straining to make out the two tiny figures growing inside of her. The technician slid the sensor back and forth across her belly, searching for better angles to look at each fetus. She adjusted some settings on the machine, performing a series of measurements and capturing still images from various different perspectives. *Do you want to know the sex?* she asked.

Courtney looked at Tim and nodded. *Yes.*

The technician smiled. *You're having two girls.*

Joy washed over Tim and Courtney. *Twin girls! And everything looks normal!* Yet Courtney was not just an expectant mother—she was a biomedical researcher. Within moments, she began to think about her pregnancy like, well, a scientist. *So I'm having twins. How, exactly, did that happen?*

By midway through the second trimester, the Griffins got used to saying it out loud: "We're having twins."

She rushed back to the lab. Working in the field of developmental genetics, she knew plenty about the processes driving embryonic development. But now she wanted to learn all she could about her own pregnancy. And she quickly discovered that twins had bred their own sub-genre of scientific literature.

Twins occur in about 1 in 50 pregnancies. Non-identical or fraternal twins, the more common form, are a product of the ovaries mistakenly releasing two—rather than one—egg for fertilization. Different sperm cells fertilize each egg, which is why fraternal twins don't look exactly alike and often aren't even the same gender. Studies have found a genetic component to fraternal twinning, so it can run in families. Factors such as advanced maternal age and in vitro fertilization can also lead to higher rates of fraternal twins. Yet neither of these issues was present in Courtney's pregnancy.

The ultrasound had revealed that the Griffin twins shared a single placenta. This almost certainly meant that the twins were identical. Unlike fraternal twins, identicals begin as a single fertilized egg. At some point in the first week or so after fertilization, that egg splits into two separate eggs during cell division. Although people commonly believe that identical twins run in families, researchers have yet to find any evidence that genetics play a role. Indeed, as far as scientists can tell, it's simply a random phenomenon.

Researchers, though, have figured out that the earlier the egg splits into two, the more independently the eggs will develop in the uterus. For Courtney, the ultrasound showed that from a single placenta ran a pair of umbilical cords, one to each fetus. Those cords delivered nourishment to the growing babies, each of whom resided in her own amniotic sac. That meant the egg had likely split four to six days after fertilization—too late to develop separate placentas to feed each embryo, but early enough still to form distinct, fluid-filled membranes to protect each of the Griffins' soon-to-be-daughters. *This*, Courtney discovered, *is a very good thing.*

Had the egg split any later, the twins likely would have shared not only a placenta but also a single amniotic sac. In such close quarters, the umbilical cords can easily become entangled. If that happens, the pregnancy comes to a sudden and devastating end.

For weeks, Courtney consumed information about twins. She also learned plenty by joining a local Mothers of Multiples group. Of course, these hardened veterans of raising twins (and triplets) spent less time discussing the genetics of multiples than the more practical aspects of preparing for them. They gave her advice that just about every expectant mother hears. *Get the nursery ready now,* they told her. *Learn how to use the car seats before the babies arrive.* But they also told her about companies that would provide free cases of formula or coupons for disposable diapers. *Just tell them you're having twins.* Membership in the "multiples club," it seemed, also carried some unexpected benefits. *Be ready. When the babies are born, you and your kids will be treated like rock stars.*

Almost anything they might need, the Griffins found, they could find through multiples club channels. An extra crib? Check. Changing table? Double stroller? Done.

As the young couple adjusted to their new reality, they got used to saying it out loud: *We're having twins.* Tim felt the babies kick for the first time. At their next ultrasound, he and Courtney watched as one twin sucked her umbilical cord while the other kept her thumb firmly planted in her mouth. The tech took some measurements. *Twin A weighs 14 ounces. Twin B is 13 ounces.*

Delancey (left) and Olivia Griffin, photographed at home with their parents on October 15, 2013, celebrated their 10th birthdays this past summer. They're now fifth graders at Wilson Elementary School in Oklahoma City.

The fetuses were growing rapidly and beginning to move and act like babies. It was, Courtney and Tim decided, time to name them. *Goodbye, Twin A and Twin B. Hello, Olivia and Delancey Griffin.*

The second and third trimesters represent a sort of paradox. On one hand, the period from 13 weeks of pregnancy until birth represents a time of unprecedented growth. Over that time, the fetus will stretch from roughly an inch-and-a-half long to 20 or so inches, and its weight will increase from an ounce or 2 to its birth weight of 5 to 10 pounds.

Yet, from a developmental biology perspective, the most exciting days have passed. "The first trimester is when you see the greatest transformation, going from a single cell to a fetus with fully formed organs, body systems and extremities," says Dr. Gary Gorbsky. "The growth and development that take place in the second and third trimesters are, in many ways, simply the consequences of the processes that were set on track during the first 12 weeks of the pregnancy."

In the second trimester, the skeleton forms into bones. The eyes, at first on the side of the head, migrate to the front of the skull. The ears drop, begin to stand out on the sides of the head, and then the baby begins to hear.

By the time of Courtney's second ultrasound—at 22 weeks—Olivia and Delancey had become noticeably active. This phenomenon, known as "quickening," comes about thanks to a functioning nervous system and developing muscles calling out for some exercise. The increasingly cramped quarters of the mother's uterus serve as a sort of gymnastics training ground for the babies, as they wiggle and twist in a cocoon of amniotic fluid. The watery fluid provides a weightless environment, a sort of cushion to protect growing children. Fetuses breathe the liquid in and out, helping the lungs strengthen and develop properly.

Amniotic fluid also helps support the umbilical cord, which pumps food and oxygen into babies' bodies. This direct delivery mechanism is one way a mother's habits, from what she eats to what she breathes, can affect her unborn child. But this impact is not limited to mom; the past behaviors of the father and generations of ancestors on both sides of the family can affect the child's health in unseen, unfelt and, until recently, undetected ways.

At OMRF, Dr. Courtney Griffin is studying this emerging field, known as epigenetics. "Behaviors such as diet, exercise and tobacco use create chemical markers that can cover the DNA," explains Griffin. Although the DNA—each person's essential genetic blueprint—remains unchanged, the chemical markers obscure certain portions of the blueprint, changing the way the body reads that plan.

"Once the epigenetic marks are there, they can stick like glue and pass on for generations," says Griffin. Worst of all, they become heritable, carried by both males' sperm and females' eggs. So the choices young people make may not only affect children they've yet to conceive—they may also impact their children's children and generations beyond.

For example, a recent study published in the journal *Human Molecular Genetics* discovered a distinct epigenetic "footprint" in smokers. Compared with people who'd never smoked, the smokers showed different patterns of epigenetic markers on

20 different regions of their DNA. When the researchers extended the analysis to a separate group of patients and mice that had been exposed to tobacco smoke, they narrowed down the epigenetic modifications to sites in four genes previously linked to cancer. The scientists suspect these changes will increase the activity of these genes and, hence, the smokers' chances of developing cancer. At this point, it's still too early to say whether the smokers' children (and grandchildren) will show the same epigenetic footprint. But, Griffin says, "Already in laboratory animals, we're seeing that these types of marks are passed from one generation to the next."

Of course, despite the rapid development of its brain during the third and final trimester, which begins at 28 weeks, the fetus remains unaware of complex biological notions such as epigenetics. Yet by this time he or she can blink, close the eyes, turn the head, grasp firmly and respond to sounds, light and touch. As the baby grows, movement often diminishes due to the tight space. In the final weeks of pregnancy, the baby drops down in the mother's pelvis to prepare for delivery.

Today, many otherwise healthy pregnancies are deliberately ended early by induced labor or Caesarean delivery. Studies have shown that as many as one-third of elective deliveries now occur before 39 weeks. But research has shown that with each decreasing week of gestation below 39 weeks, there is an increased risk of complications like respiratory distress, jaundice, infection, low blood sugar and even death.

"If there are no medical complications, the healthiest outcome is delivery at 40 weeks," says Dr. Stephen Prescott. But, he says, this is not to suggest that women should panic if natural labor occurs earlier. "When labor begins on its own, that's a whole different story."

In the summer, the North Carolina air takes on the consistency of stew, a hot gruel more suited for eating than breathing. *I could not*, thought Courtney Griffin, *have picked a worse time and place to be pregnant. With twins.*

A few weeks into her third trimester, Courtney's lab moved. That meant lots of time on her feet, packing boxes and hauling scientific equipment and supplies. Her feet and ankles had blown up like marshmallows. With an added 40 pounds—and counting—each step felt like a needle jabbing into her hips.

Then came the contractions. *This can't be it!* she thought when she first felt a marked tightening in her belly. *I'm only at 31 weeks.* But soon enough, the sensation subsided. A wave of relief washed over her. *These must be Braxton-Hicks contractions.* Courtney had read about these "false" contractions that could come several times a day in the final trimester. They began to come and go so frequently that she almost got used to them. *This isn't the real thing,* she'd reassure herself each time. Still, there was always a chance. *I've made it this far. Please just let me hang in there little bit longer.*

At her 33-week appointment, Courtney's doctor voiced concerns about her swollen feet and ankles. *Plus, you've put on 10 pounds in the last two weeks. You're retaining a lot of water. Let's try some light bed rest for a week.*

Courtney liked the sound of that. Heck, she was napping all the time anyway. *A little R and R might be just what I need.*

Even in bed, though, Courtney's hips kept her in constant pain. Sitting was almost as uncomfortable as standing, and lying down wasn't much better. An ultrasound showed that by 34 weeks, the babies each weighed about 4½ pounds. Olivia's head was positioned low in Courtney's pelvis, pushing on her hip. Which explained the pain.

Yet as uncomfortable as she was, Courtney knew that every day she could forestall delivery lessened the chance of complications. Twins usually arrive early. When an extra fetus occupies a space designed for one, the uterus swells, triggering early labor. With twins, that typically occurs at 36 weeks.

For Courtney, it happened on the first day of her 35th week. In the wee hours of July 12, 2003, she felt the telltale wetness. *My water just broke.* It didn't happen quite like in the movies, where there's an obvious gush. But there was no doubting it: The amniotic sac in which the twins had resided for the past eight months had ruptured. Labor had begun.

Just as pregnancy differs for every woman, so does labor. For Courtney, it took 10 hours for her body to push Olivia from her uterus. In another three minutes, Delancey arrived.

Moments later, Courtney cradled her two, healthy newborn daughters, one in each arm. No more worries about test results. Complications. High-risk pregnancies or birth defects. Trillions of cells had divided. Organs had formed. And out had come these living, breathing creatures.

The scientist in Courtney understood that this was no miracle. Sure, there had been a few detours along the way—hello, twins—yet in the end, everything had worked just as it should have. Still, as a new mother, she couldn't help but feel awe. And joy. *Now*, she laughed to herself, *all we have to do is raise them.*

7 Things You Didn't Know about

Grad Students

No, OMRF is not a university. But with more than 30 graduate students from the University of Oklahoma Health Sciences Center and other state institutions working in our labs, it can sometimes feel like one. OMRF senior scientists train the students, each of whom is working toward a Ph.D. The process typically takes four or five years. Along the way, students learn the ins and outs of biomedical research, and the scientists get the help of energetic workers with fresh, new ideas.

I knew I wanted to be a scientist when I was inspired by a really good biology teacher.

Flora Ling
Hometown: Tulsa

You think about your experiments, papers you need to be reading or things you should be writing all the time. There are times I even dream about them.

Joe Wilkerson
Shattuck

How do I juggle my school and work schedules? Simple—by eliminating sleep and a social life.

Eric Dumas
Watonga

If I couldn't be a scientist, I'd be a race car driver.

Reema Biswas Davis
Pune, India

I want to find a cure for alpha-antitrypsin deficiency. My sister and I both carry a severe form of this disease, and she is on the liver and lung transplant list.

Julie Ward
Oklahoma City

The hardest part of my work is when experiments fail. I just spent a year optimizing and running experiments for a project that ended up proving my hypothesis was wrong.

Lori Garman
Enid

Once I made a potato launcher fueled with propane and oxygen. On about the 50th launch, the whole thing exploded. My parents thought I was probably dead.

Lee Bockus
Oklahoma City

Want hear more from our grad students?
Go to omrf.org/FindingsExtra

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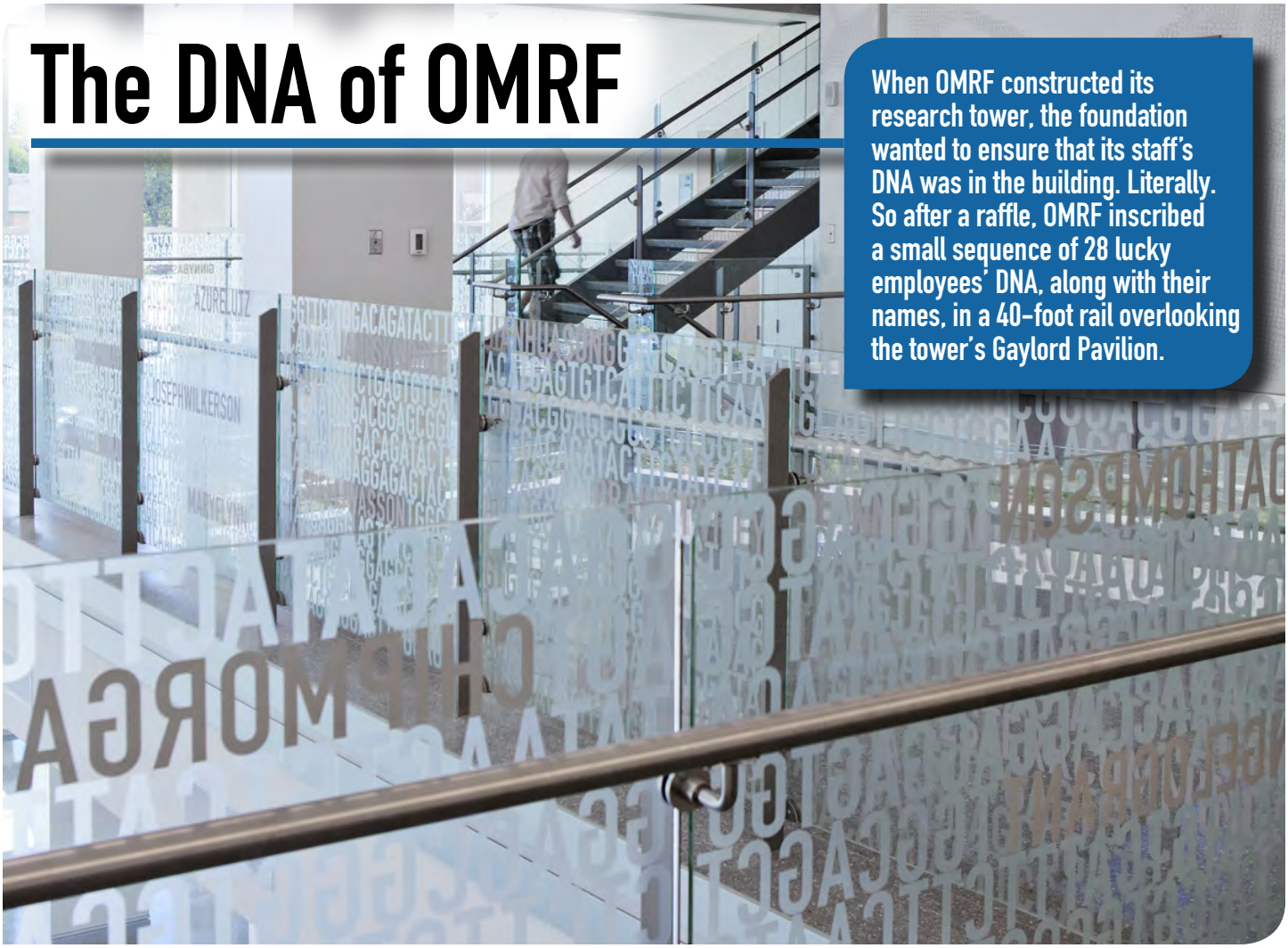
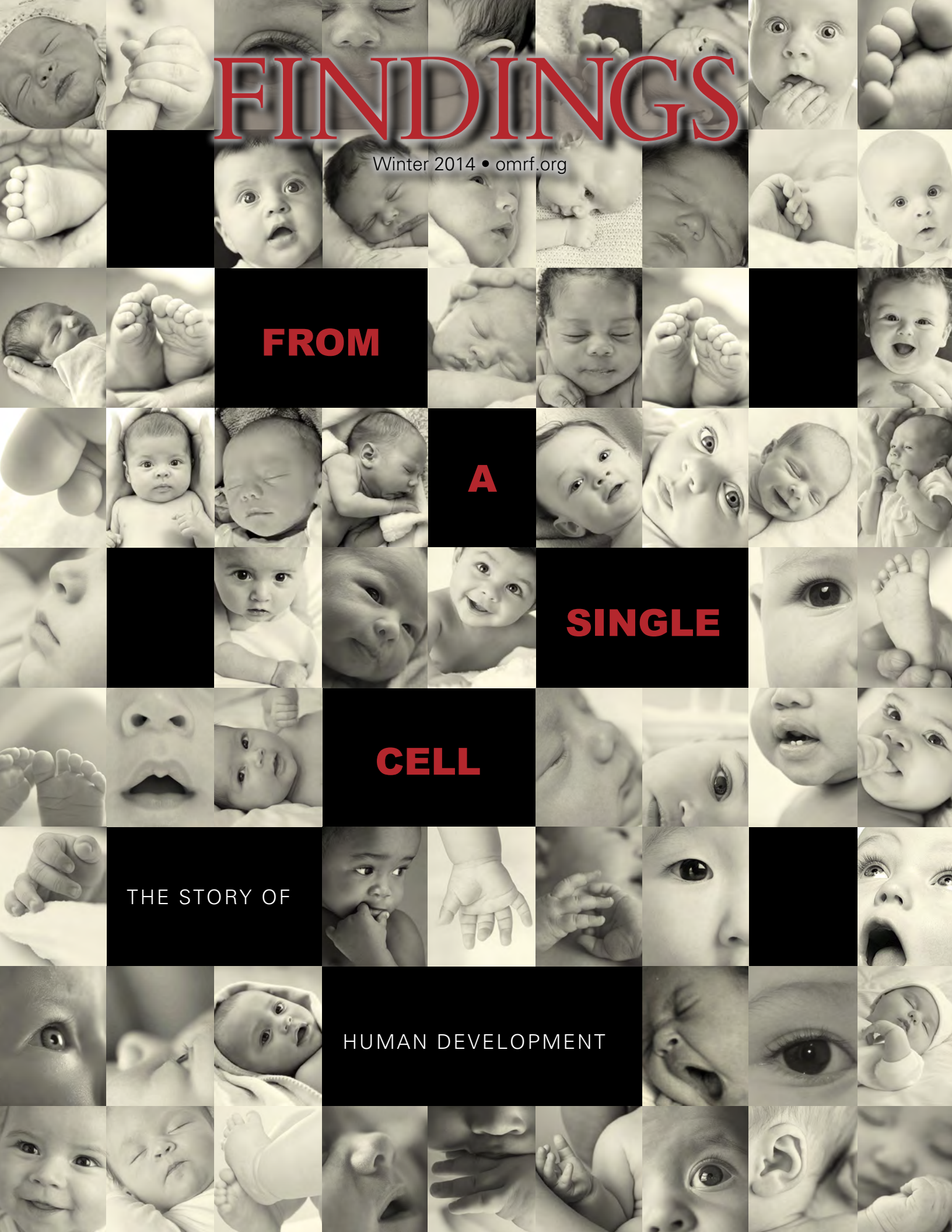


When OMRF constructed its research tower, the foundation wanted to ensure that its staff's DNA was in the building. Literally. So after a raffle, OMRF inscribed a small sequence of 28 lucky employees' DNA, along with their names, in a 40-foot rail overlooking the tower's Gaylord Pavilion.



FINDINGS

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FROM A SINGLE CELL

THE STORY OF HUMAN DEVELOPMENT