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Examine a problem from a different vantage point can often lead to valuable and unexpected insights. In the realm of biological research, new visualization technologies advance our understanding of life by revealing what was previously hidden or unnoticed.

Programs like Google Earth now enable an unprecedented level of immersion in faraway places that we may never get to visit in person. These geobrowsers combine ground, aerial and satellite images to allow us to explore and examine physical features of our planet. The ability to pan, zoom and rotate our view of a three-dimensional representation of the world provides anyone with a web browser the opportunity to explore the world with a whole new level of breadth and depth.

Technologies based on similar principles are now helping biologists gain a new perspective on the subjects of their investigations. For instance, highly detailed three-dimensional digital models of tissues and organisms can now be built by combining hundreds or thousands of individual microscopic images. Using a geobrowser-like program, researchers explore the reconstructed models at a macro scale and then zoom in on particular regions of interest with astonishing detail.

This issue’s cover story gives a glimpse into how Stowers researchers are using visualization technologies to study biological systems from new vantage points. One of these projects involves the high-resolution imaging of the planarian flatworm, an organism well known for its exceptional regenerative capabilities. The ambitious goal of these studies is to create an interactive representation of the entire animal in order to reveal new relationships between structure and function and to provide a baseline reference for future studies. Other visualization projects focus on how the structure of a particular protein complex helps chromosomes sort properly and how cancer stem cells are recruited to repopulate tumor tissue after treatment relapses.

Such bold undertakings benefit from the type of teamwork that abounds at the Institute. The Institute’s thirteen scientific support facilities and centers are key leaders in the Institute’s efforts to apply new technologies to biological problems. Interspersed with investigator labs on campus, the scientific support groups offer a wide variety of services and collaborative opportunities, such as DNA sequencing, computational analysis, and high-resolution imaging.

New ways of seeing things can come not only from a new set of technologies but also from a new set of eyes. Each year, the Institute benefits from the fresh perspectives of an elite group of undergraduate summer scholars performing hands-on research in labs across the Institute.

Year after year, we are amazed by what these budding scientists are able to absorb and achieve during their time at the Institute. Another article in this issue introduces you to some of these scholars and describes how their infectious enthusiasm and passion boost everyone’s energy level each summer.

As you read through the pages that follow, I hope you enjoy learning about some of our latest research findings and some of the people who make the Institute a very special place to work.
UNCHARTED TERRITORY

Navigating New Biological Terrain with Teamwork and Technology

By Marla Vacek Broadfoot
During the Age of Exploration in the fifteenth and sixteenth centuries, a rush of European explorers set out to find fabled lands such as the gold and spice islands of Asia. Many of these sea travelers, however, embarked on their voyages under a number of misconceptions. The best map in the late fifteenth century indicated that Asia was much larger, and closer to Europe by water, than was actually true. When the explorers ran upon solid ground again—landing on an island perhaps, or the coast of North or South America—they often had no idea where they were. It wasn’t on the map.
Today, it is hard to imagine such a mind-bending revelation. Centuries of exploration and documentation have charted practically every mountain, valley, and waterway, and the recent introduction of global positioning system (GPS) satellites and smartphones has allowed us to zero in on any location, cruise down any street, peek into any yard. Yet there is plenty of uncharted territory left to explore. Out in the cosmos, astronomers are discovering new planets. Under the seas, marine biologists are identifying new species. Deep inside cells, biologists are mapping new structures and molecular interactions, with unprecedented precision.

Much like GPS revolutionized our understanding of geography, the advent of robotics and miniaturization is enabling scientists to see a part of ourselves that we might not have known existed. At the Stowers Institute, laboratory researchers are working side by side with scientific support teams to plot the unknown. It is an exciting time marked by technological sophistication and eye-opening insights. And it is moving at a dizzying pace.

“We can’t get enough,” says Alejandro Sánchez Alvarado, PhD, an investigator at the Institute and a frequent collaborator with the Institute’s scientific support groups. “It’s like discovering new terrain on a regular basis.”

A FANTASTIC VOYAGE

As the needs of the Institute’s research programs have emerged and evolved over the past decade and a half, Stowers scientific support groups have grown and adapted as well. Two of these groups—Histology and Electron Microscopy—have experienced several similar transformations in their parallel growth trajectories at the Institute. And, as is the norm for Stowers scientific support groups, their paths intersect regularly in the course of seeking answers to biological questions.

The fields of histology and electron microscopy have been around for a long time. Histology was developed in the mid-1800s, when scientists discovered that they could use a variety of dyes to stain different parts of cells—and cell types—in glittering shades of purple, pink, blue, gold, and silver. Electron microscopy came much later, in the 1930s. Instead of using light to image a specimen, electron microscopes use beams of electrons, which have much shorter wavelengths and thus can reveal the structure of smaller objects. Both methods were incredibly tedious and time-consuming, and over the decades, started to show their age. Then, at the turn of the last century, these relatively old technologies began to incorporate advances in computer science and automation, making them more valuable than ever before.

Tari Parmely came to the Stowers Institute in the midst of this renaissance. The native Kansan began working as a research specialist in the laboratory of Joan and Ron Conaway in 2002 and took over the management of the Tissue Culture Facility in 2008. In 2009, she added Media Prep (which prepares nutrient broths and agars for growing microorganisms) and in 2010 added Histology and Electron Microscopy.

Back then, the Histology Facility was staffed by several talented histotechnologists, who had been trained primarily in a hospital setting. But at the Institute, scientists don’t just deal with human tissue. They work
with a multitude of model systems—flatworms, sea anemones, mice, yeast—and the list keeps growing. Every organism is different, and every tissue is unique. Each time a new model system comes online, the group has to develop or refine processing techniques to optimize the images that they produce for the researcher. So one of the first things Parmely set out to do as the head of Histology was to add research expertise to the lab.

Parmely found this expertise in Yongfu Wang, PhD, an assistant research professor at the University of Kansas who was well versed in both histology and research. “The rest of the team really welcomed him, and they have all worked so well together,” says Parmely. “It has been a beautiful thing to see. He has expanded the lab’s capabilities with molecular histology techniques, and that has helped the lab evolve into a more collaborative space.”

The Electron Microscopy Facility has also grown under Parmely’s stewardship. Initially, the facility consisted of a microscope, an ultramicrotome (the instrument used to cut specimens into thin slices for imaging), and Fengli Guo, PhD, a specialist to operate them both. The group has expanded to include three specialists and a technician, along with new equipment and technology. Today, the facilities can do much more than process samples—they can help researchers plot the course of their experiments, and provide the latest tools to ensure smooth sailing along the way.

Investigator Linheng Li, PhD, is interested in exploring the environment in and around tumors that allow cancer to relapse. For the last several years, he has focused his attention on a special type of cell known as the cancer stem cell, notorious for its ability to rebuild tumors decimated by chemotherapy and radiation. Xi (CiCi) He, MD, a senior research specialist in Li’s lab, worked with both the Histology and Electron Microscopy Facilities to examine tumors from a mouse model of colorectal cancer. She recalls the team being just as devoted to the project as she was. “They were very collaborative. Sometimes we finished an experiment late in the evening, after the staff had gone home, but they came back to fix the sample, so we could get it under the microscope quickly,” says He.

There, amid the dying cells, He witnessed an amazing rescue attempt undertaken by an unlikely ally: macrophages, the white blood cells that swarm to sites of infection and injury and gobble up cellular debris. The cells that were being killed off by chemotherapy and radiation sent out distress signals to macrophages, which in turn recruited cancer stem cells to produce more tumor cells. He showed that these signals could be blocked by a clinically approved drug called Celecoxib, that when combined with traditional cancer treatments could reduce tumor size and tumor number—and prevent the drug-resistant cancer stem cells from spawning a relapse.

“It was an amazing discovery, and they made it together,” says Li. “The core facility members have ownership of the work, too.”
INTELLECTUAL EXPLORERS

With scientific knowledge accumulating at an exponential rate, researchers and specialists at the Institute have to make a concerted effort to keep up. Parmely feels it is important that members of scientific support teams hone their intellect by attending lab meetings, reading the literature, and participating in conferences. Some might attend conferences that feature advances in a specific technique, such as fluorescence in situ hybridization, whereas others might frequent larger gatherings that cover an entire discipline, like the National Society for Histotechnology annual meeting. The staff will pop in regularly to various meetings and seminars taking place within the halls of the Institute to find out what kinds of scientific questions are under investigation.

Ideas also bloom from conversations between researchers in different scientific support groups. Last year, Zulin Yu, PhD, a specialist in the Microscopy Center, which focuses on light microscopy techniques, mentioned to Wang in Histology a paper detailing a new technique called expansion microscopy that allows tiny structures to be visualized with nanoscale precision. Imagining how Stowers research projects might benefit from this approach, Yu and Wang set out to bring this technology to the Institute. Parmely recalls Wang tracking down and querying one of the inventors of expansion microscopy at a national meeting. “Yongfu was so excited about the technique,” she says. “He wanted to know every detail.”

Their determination and persistence paid off. With enabling contributions from a number of other Stowers colleagues in an impressive example of teamwork, Yu and Wang worked with Cori Cahoon, a predoctoral researcher in Investigator Scott Hawley’s lab, to apply the technique to a protein structure too small to be visualized by even the most high-power microscopes. That structure, known as the synaptonemal complex, is essential for the correct sorting of chromosomes into eggs and sperm during reproductive cell division or meiosis. The team gathered samples of the synaptonemal complex from dissected fruit fly ovaries, embedded the samples in a special type of gel, added liquid, and watched the samples expand fourfold. A key technical achievement by Wang was refining the sectioning procedure to allow the samples to be cut into thin slices prior to the fourfold expansion, thus permitting the use of advanced imaging techniques. When they put the samples under the microscope, they found that the structure looked like two sets of railroad tracks, one stacked on top of the other.

“The structure was so much more complicated and beautiful than we ever imagined. It completely changed the way we think about this structure and what it does,” says Hawley. “What they accomplished was a technical tour de force.”

NEW WORLDS

Mapping nano-sized structures and charting the interior of living organisms once seemed like impossible tasks. But recent technological advances are making the impossible possible. For twenty years, Sánchez Alvarado has studied planaria, arrow-shaped flatworms known for their amazing regenerative powers. These creatures embody an ideal system for understanding how some organisms regrow damaged organs or missing...
body parts. Sánchez Alvarado has long dreamed of digitally reconstructing the anatomy of a whole planarian, from tip to tip.

The feat—which entails dicing the miniscule worm into thousands of ultrathin sections, photographing each section individually, and then piecing the images back together again on the computer—would take a lifetime to complete with the old technology. Instead, his laboratory has resorted to analyzing a few small sections and then imagining how they might fit together to make the larger organism.

“It’s like sitting down to read James Joyce’s *Finnegans Wake*, and rather than tackling all two thousand pages, you just read every other hundred pages and assume from that sampling that you know more or less what the story is about. That’s no way to try to comprehend the whole body of work,” says Sánchez Alvarado.

Last year, Sánchez Alvarado learned about machines that could be adapted to section an entire planarian, process the sections, and stitch them together into a three-dimensional digital image. His dream project could become reality, attainable in a mere couple of years rather than a stretch of decades. Sánchez Alvarado wrote a grant to the Howard Hughes Medical Institute, which together with the Stowers Institute provided the funds to purchase the magical pieces of equipment, aptly named the *MERLIN* scanning electron microscope and the *3View* ultramicrotome.

“For months and months, we were anticipating it arriving, and it was like Christmas morning when it showed up. It was like a big shiny toy,” says Parmely.

Right away, Stephanie Nowotarski, PhD, a postdoc in Sánchez Alvarado’s lab, began working with Melainia McClain and the Electron Microscopy team to get the machine online. Within a couple of months, it was up and running, and Nowotarski was snapping pictures of epithelium, the thin layer of tissue that covers the surface of the organism. The technology incorporates ATLAS.ti software, a sort of Google Earth app for electron microscopy that enables the user to zoom in and out on samples with varying degrees of magnification. When she shared her results at a lab meeting, she started by showing an image of a whole planarian worm, which is about the size of a toenail clipping. As she zoomed in further, she brought into focus the pores on its surface, and a gasp echoed throughout the room.

“It really is a team of equals here, and this collaboration opens the door to discovering new biology that we may not even know has been there under our noses the whole time,” says Sánchez Alvarado.

For example, Sánchez Alvarado says that scientists still don’t know how many cell types, or even how many individual cells, make up the human body. Is it 15 trillion? 70 trillion? What do they each look like, and how do they behave? By mapping the architecture of simpler systems like mice, fruit flies, and flatworms, researchers can set the course for creating a better understanding of the human condition.

After all, there is still much to be discovered, across the whole of biology. And science explorers could benefit from a better map.
A SUMMER TO REMEMBER

Summer Scholars Program gives undergraduates a taste of scientific life

By Anissa Anderson Orr
Summer days bring pool time, sunshine, hanging out with friends, and sleeping long into the morning for some college students. It can be a quieter time of year with a break from a busy school schedule. But for other students, summer days bring lab research, exciting discoveries, and a one-of-a-kind scientific experience.

At the Stowers Institute, as temperatures rise and summer kicks in to full swing, the campus buzzes with energy. Each summer, the Institute welcomes between 30 and 40 undergraduate students as part of the Stowers Summer Scholars Program. You can hear them sharing a laugh over lunch in the cafeteria, reveling over a new discovery in the lab, or cheering together at a Kansas City Royals game. They come from schools all over the country and the world—bringing an unbridled passion for science that’s impossible to miss.

“The interaction with undergraduate students and their excitement—it really livens up the summer,” says program coordinator Ana Pedraza, PhD, associate dean for academic affairs for the Graduate School of the Stowers Institute for Medical Research. “That energy translates to everybody at the Institute.”

**Hands-on experience**

Nearly 300 students have been trained through the Summer Scholars Program since its start in 2004. Funded by the Stowers Foundation—an entity distinct from the Stowers Institute that supports unique educational programs—the program fulfills a mission to introduce promising young researchers to graduate-level, cutting-edge research, and to recruit students for the Institute’s graduate school.

“Scholars get a glimpse of the limitless potential that the Stowers Institute fosters,” Pedraza says.

Summer Scholars spend eight weeks immersed in a research topic under the direction of a principal investigator. The program is open to undergraduate students currently pursuing a degree in the biological or physical sciences. Stowers investigators and lab members select candidates whose skills and interests best match their labs.

“The strengths that Scholars bring to the program are as varied as the labs themselves,” Pedraza says. “This is helpful because it diversifies whom we accept. Every faculty member has their say on who is accepted in the program.”

Scholars have a summer packed with hands-on experiences, learning from scientific leaders at the top of their fields. They interact and collaborate with other members of their laboratory and the Stowers community, and in the process, experience the intellectual and collaborative spirit of research. They learn innovative techniques in laboratories and core centers, which are equipped with the latest technology.

During the eight weeks, Scholars spend most of their time in the lab, where they work full-time, supervised by a mentor. All Scholars attend weekly lunches that feature a scientific seminar on a variety of topics presented by principal investigators or predoctoral researchers.

“They love the seminars because it helps give them a broader view of what’s going on in the Institute,” Pedraza says. “They are informal and intimate and give our scientists a chance to present their research in a way that is more understandable at the undergraduate level.”

The program also provides the Scholars the opportunity to talk about their own work. “Anyone in science will tell you that communicating your work is a critical component of doing science—and it can be daunting at first.” Pedraza says. Scholars present their summer work to their lab members at lab meetings and then to a larger forum at an all-Institute poster session. Family and friends are also invited to see how much they’ve accomplished.

It is an intense program, but there is a strong effort to balance work and play. To build a community among their peers and colleagues, Scholars also socialize outside the Institute. This summer, planned social events included an escape room challenge, a bus tour of Kansas City, and visits to an amusement park, a baseball game, the Kansas City Zoo, and other area attractions, as well as occasional movie nights and weekly social gatherings.

“We want them to build a sense of community and give them well-deserved breaks,” Pedraza says.
**Student experiences**

This year’s Summer Scholars came from far and wide, representing 11 states, and eight countries outside the United States.

For Renny Ma, coming to the Stowers Institute was both a new adventure and a sort of homecoming. Ma grew up in the Kansas City area and attended a biotechnology program in high school, sparking her interest in basic science. Now she’s earning her BS degree in neuroscience at Brown University. During her winter break she worked in the lab of Stowers Investigator Ron Yu, PhD, who studies sensory systems in mice. At Yu’s encouragement, Ma returned for the summer as a Summer Scholar.

Ma’s research focused on the role of mouse pheromones in aggression or mating—responses necessary for survival or reproduction. She studied how pheromones could influence certain types of mice that are sociable but poor nest builders. The work sheds light on the fundamental neural pathways and mechanisms involved in development and behavior.

Ma says her experience exceeded her expectations. She accomplished a lot, enjoyed her experience, and was especially impressed by the spirit of collaboration and exploration, both inside and outside the lab.

“Dr. Yu and Limei Ma [no relation], who is a research scientist in his lab—both of them really encouraged us to ask a lot of questions, and not just simple ones, but to dig down deep.”

Ma headed back to Brown armed with valuable new skills.

“During my time at the Institute, I learned an incredible amount about problem solving, and how to approach a problem from beginning to end,” she says. “And I think in pursuing my studies, that will be really useful.”

The journey to the Stowers Institute was much farther for Maxime Killer, who is earning his MS degree in biochemistry and molecular biology from the Université Pierre et Marie Curie in Paris, France.

Killer learned about the Summer Scholars program from a visit to his Paris campus by Stowers Investigator Paul Trainor, PhD, who encouraged his interest in proteins and proteomics. Killer was intrigued by the opportunity of working in the lab of Michael Washburn, PhD, director of the Stowers Proteomics Center. He applied to the program, and was accepted.

Working with Postdoctoral Research Associate Mark Adams, PhD, Killer used mass spectrometry and other techniques to explore how the protein SIN3 recruits other important proteins that regulate gene expression—the process of switching genes on or off. The way gene regulators are recruited is critical for the fate of a cell, and defects in this process can lead to metabolic diseases and cancer.

Killer appreciated having the tools, technologies, and expert guidance for his research readily available, including a state-of-the-art mass spectrometer.

“I was trained to use a machine that was one of the best on the market and probably worth millions of dollars. And they let an intern like me use it. You don’t always get that kind of access at other institutions,” Killer says.

Now back in Paris, Killer says the experience taught him how to organize his time and learn how to plan for unexpected failures in research. Conversations with colleagues improved his fluency in English, which will help him communicate to more audiences as a future member of the international scientific community. He also built solid relationships with Stowers scientists, who are helping him secure other internship opportunities.

“I would definitely recommend the Summer Scholars program to international students,” he says. “Everyone is supportive, and they do their best to help you succeed.”
The faculty perspective
Faculty who host Scholars in their labs appreciate the chance to mentor up-and-coming scientists who reinvigorate their labs with new ideas and fresh perspectives.

“The students are really talented, and having them here gives the lab a splash of something fresh, and changes things up a bit,” says Stowers Associate Investigator Julia Zeitlinger, PhD. Her lab focuses on uncovering the rules that govern gene regulation.

The program also gives predoctoral researchers in her lab a valuable mentoring experience when they are paired with Scholars. And it is a good opportunity to test out scientific talent, and recruit the best of the bunch for the Graduate School.

Zeitlinger hosts students in her lab each year. She considers herself “very selective,” and interviews each candidate by video call to determine if they have the right skills and personality for her lab. Zeitlinger is drawn to students who are curious, ask a lot of questions, and have taken the time to educate themselves about her work.

“If they have an analytical feel and drive, that is when I think they will do well,” she says.

This year, Zeitlinger hosted three Scholars who came from Russia, Ukraine, and Mexico. They helped launch new genomic sequencing and imaging technologies for studying fruit fly embryos. Zeitlinger says their preliminary work was essential to getting the projects off the ground.

Students who demonstrate excellence in the lab are rewarded with the kind of recommendations, research experience, and connections critical for launching scientific careers.

“With the Summer Scholars program, we are providing a nice springboard for young talented scientists,” Zeitlinger says.

Coming back for more
It’s not uncommon for Summer Scholars to return to the Institute to work on their senior thesis, enroll in the Graduate School, or even join the scientific staff. That’s a key indicator of the Summer Scholars Program’s success, Pedraza says.

“We hold exit interviews, and from the feedback we receive, it’s clear they get a lot out of it. They learn how to be a part of a scientific community, excel in research, and take advantage of what the Stowers Institute has to offer,” she says, adding that the program has far-reaching benefits, not just for students or the Institute, but for scientific discovery as a whole.

“It’s a natural extension of Jim and Virginia Stowers’ philosophy. When you foster a passion for science—that’s how you advance science and find cures. And that’s our ultimate goal.”
When she’s not in the lab studying the regenerative powers of zebrafish, Stowers Investigator Tatjana Piotrowski, PhD, enjoys exploring the trails around Kansas City with her family, or hiking remote mountain paths on vacation. While Piotrowski loves the busy and collaborative environment at the Stowers Institute, she also relishes getting off the grid. Nature regenerates her.
“You might meet three people in the whole week that you’re out there on a nature trek. That’s something I love very much,” she says.

Piotrowski credits her upbringing in the picturesque, medieval town of Herrenberg, near Germany’s Black Forest, for her love of the outdoors, and for sparking her interest in science.

“I grew up in nature,” she says. “The little town where I lived was surrounded by fields and orchards and creeks. We lived next to a forest, so I’d spend afternoons there after school. I guess it really made me interested in trying to understand the natural world and animals, and animal behavior. From early on, even in high school, I wanted to study animal behavior or zoology.”

Called to a scientific career, Piotrowski went on to earn her BS degree in biology and MA in zoology from the University of Tübingen, Germany. However, she performed her MA thesis work at the University of California, San Diego. It was at UCSD that she first started studying the anatomy and evolution of the nervous system of fishes. After returning to Germany, Piotrowski earned her doctorate at the Max Planck Institute for Developmental Biology, and then completed a fellowship at the National Institutes of Health’s Laboratory of Molecular Genetics in Bethesda, Maryland. In both labs she studied the genetics of zebrafish—organisms known for their transparent embryos that allow scientists to easily track development of tissues and organs.

Following her training, Piotrowski joined the faculty of the University of Utah School of Medicine. She joined the Stowers Institute in 2011 as an Associate Investigator, together with her husband, Stowers and Howard Hughes Medical Institute Investigator Alejandro Sánchez Alvarado, PhD. Today, her research focuses on the lateral line, a sensory organ in zebrafish, and the mechanisms that allow zebrafish hair cells to regenerate. It’s a field of research that offers growing insight into human development and disease.

WHEN DID YOU TRULY REALIZE YOU WANTED TO BE A SCIENTIST?
After high school, I was interested in both biology and geology. But I wasn’t sure which field I wanted to pursue. So, I went to San Francisco for a year to work as an au pair, taking care of two young boys. At the same time, I audited classes at the University of San Francisco—both biology and geology courses. I also took advantage of the university library to read scientific journals. I think that’s really when I realized I would love to do science myself, when I read all these studies that people have done. I fell in love with the idea that you could make discoveries and share them with others.

And I have to say that it was a terrific year right after high school. It was very eye-opening, and made me more self-confident. For example, when I went to university after my return to Germany I did not hesitate to walk up to professors, knock on their doors, and ask them for advice. Without having had that year where I had to rely on myself, and live somewhere else where I didn’t know anybody, I probably wouldn’t be where I am today.
WHEN DID YOU BECOME INTERESTED IN ZEBRAFISH?
I began to work on zebrafish genetics and the evolution of the lateral line when I was a master’s student in Glenn Northcutt's laboratory at the University of California San Diego. Whenever Northcutt would take a break, some other lab members and I would join him and have all these conversations about the latest scientific publications. I learned so much from those conversations. After that year, I was convinced that I wanted to pursue a career in science and study zebrafish in particular.

I went back to Germany to pursue my PhD in the laboratory of Christiane Nüsslein-Volhard, PhD, who would later win the Nobel Prize in Physiology or Medicine in 1995. I participated in one of the first large-scale screens for zebrafish mutations affecting embryonic development. During that time, almost everyone in the zebrafish field came through the lab to visit and see the screen. Students were encouraged to show their work to the visitors—often leaders in the field. That was very motivating to me as a student.

WHAT DIRECTION IS YOUR RESEARCH TAKING NOW?
We’re trying to understand how sensory hair cells in the lateral line develop and how they regenerate after damage. These sensory hair cells are like hair cells that we have in our inner ears for hearing. However, in mammals, such as ourselves, these cells die from aging or after noise exposure, and they never regenerate. In contrast, in chickens, amphibians, reptiles, and fish, new hair cells are constantly generated.

We’re performing single cell expression analyses right now to see which genes are active in each cell. This allows us to determine which cell is talking to another cell to ensure that one cell turns into, for example, a hair cell, while the neighboring cell will be a support cell. All these decisions involve cells communicating with each other. Importantly, our studies will hopefully teach us how zebrafish hair cells regenerate, providing us with clues of how to trigger hair cell regeneration in mammals in the future.

WHAT MAKES ZEBRAFISH SO INTERESTING TO STUDY?
The beauty of the zebrafish system is that we can watch this regenerative process happen in a live animal, which is not so easy to do in, for example, a mouse or a chicken. We can watch how a stem cell behaves under normal conditions. We can also manipulate genes, change the function of genes, and then watch the cells again and see how these genes influence the behavior of individual cells.

Watching these cells develop and regenerate in time-lapse movies is really, incredibly beautiful. One always observes and discovers unexpected cell behaviors. That’s why research is so much fun, because you constantly see new things that nobody else has seen before.

WHAT’S IT LIKE HAVING TWO SCIENTISTS IN THE FAMILY?
It’s great because we can exchange experiences, and ask each other for advice. I don’t think we ever get bored talking with each other. We understand each other’s passion for science. If I wanted to go check on an experiment in the middle of the night, it would be OK. And vice versa.

On the other hand, when our kids were little (they’re now teens), they were sometimes a little annoyed when we had our science conversations. Sometimes they even thought we were fighting with each other, until we explained that we weren’t fighting over personal things. We were just having fun discussing science.

WHAT DO YOU LIKE BEST ABOUT YOUR JOB?
What’s so fascinating about science and being a scientist is that it’s a huge puzzle. And you’re trying to solve it a piece at a time.

My job is really a lot of fun because it is challenging but also rewarding. One constantly makes new observations that one has to put into the context of what’s known. Likewise, colleagues in the field publish their results and one has to see how your results fit into that. Do your colleague’s findings contradict your results, or add to them, or do they push the interpretation into a different direction? It’s like a detective story that never ends. 😊
Cancer cells may streamline their genomes to proliferate more easily

Researchers in the laboratory of Investigator Jennifer Gerton, PhD, have provided evidence suggesting that cancer cells might streamline their genomes in order to proliferate more easily. The study shows that cancer genomes lose copies of repetitive sequences known as ribosomal DNA. While downsizing might enable these cells to replicate faster, Gerton suspected that this streamlined genome would come at a cost.

Previous studies on budding yeast showed that whittling down the number of copies of ribosomal DNA created a genome that was very sensitive to DNA damage, so to see if this same result held true in higher organisms, Gerton’s team treated cancer cells from mice with four different DNA-damaging drugs. They found that the cancer cells were more sensitive to DNA damage than normal cells. They believe this weakness could potentially be exploited by DNA-damaging chemotherapeutics. “If what we found in mice holds true for human cancer, it could be very useful in the clinic,” says Gerton.

The findings were published June 22, 2017, in PLOS Genetics.

Selfish gene acts as both poison and antidote to eliminate competition

In collaboration with Fred Hutchinson Cancer Research Center researchers, Stowers researchers identified a gene found in fission yeast that acts as both a poison and an antidote to ensure its transmission into the next generation, and to eliminate its competition. Stowers Assistant Investigator Sarah Zanders, PhD, and colleagues detailed how the parasitic selfish gene S. kambucha wtf4 destroys developing gametes (analogous to sperm) that don’t possess it. The gene poisons developing gametes, but keeps the antidote for itself. Zanders likens the mechanism to a dinner party in a murder mystery novel, in which everyone, including the host, is poisoned, but the host has the antidote.

Gametes that inherit the selfish genes are protected because they have the antidote. The gametes that don’t inherit the selfish genes are destroyed. According to Zanders, the study expands the current knowledge of the nature of gamete-killing meiotic drive genes and how they can contribute to infertility. The finding may also guide future discoveries of meiotic drive genes in other organisms, such as crops or humans.

This report was published June 20, 2017, in eLife.
In meiosis, the cell copies all its chromosomes, pairs them up, and then divides them into eggs or sperm. This carefully choreographed process is helped along by the synaptonemal complex, an assembly of proteins that forms between the paired homologous chromosomes and keeps them properly aligned and in position. Errors during meiosis are a leading cause of miscarriages in humans.

In a recent report, scientists in the lab of Investigator Scott Hawley, PhD, along with other Stowers colleagues, describe the three-dimensional structure of a protein complex that is essential to meiosis. By merging two advanced microscopy techniques, the researchers discovered that this structure, known as the synaptonemal complex, looks like two sets of railroad tracks stacked on top of each other.

“This was a really incredible insight, a technical leap using this new methodology of expansion microscopy and merging it with structured illumination to create a way to look at a structure that hasn’t been resolved before,” says Hawley. “There is a lot more we can learn. The deeper we dive into structure, the more complexity we see, the more amazing the structure becomes. Structure provides so much insight into function.”

This work was published online July 31, 2017, in the Proceedings of the National Academy of Sciences.
Stowers researchers examined the relationship between two regulator genes—Nanog and Hox. Nanog regulates a cell state called pluripotency, where a cell has the ability to self-renew and the potential to change into any of a number of cell types. Hox sparks cells to differentiate, or become a more specialized cell type such as a heart, brain, or skin cell. In adult organisms, striking a balance between these two states is important to keep many tissues in equilibrium. The blood supply, for example, has cells that are differentiating, dying, or being repaired, and a reserve population of blood-producing adult stem cells is needed to help replace them.

The study suggests that balance between pluripotency and differentiation hinges in part on regulatory communication involving inhibition between Nanog and Hox genes—something that compares to parents giving their children instructions. “Parents may say, ‘You need to get good grades; you need to learn this,’ for positive guidance but they are likely to reinforce the importance of that advice and minimize negative outcomes by saying, ‘You don’t want to do this,’” says Robb Krumlauf, PhD, an investigator and the scientific director at the Stowers Institute and senior author of the study.

The work provides important insight into the basic processes of tissue formation, and holds relevance for the field of regenerative medicine and the development of therapeutic approaches for certain cancers.

This study was published online June 5, 2017, in the Proceedings of the National Academy of Sciences.

In transcription, the first step of gene expression, the information stored in DNA is copied into RNA by a molecular machine known as RNA polymerase. Rather than hurriedly transcribing a gene from start to finish, these polymerases often pause as they travel down the double helix, sometimes for as long as an hour at a time. Researchers in the Zeitlinger Lab studied the effect this pausing had on the overall process of transcription. They showed that when one polymerase pauses, it keeps other polymerases from initiating transcription. They believe that these pauses could provide a much-needed respite in between bursts of transcription to make gene expression more controlled and deliberate.

“Having traffic rules makes sense. Leaving polymerase traffic to randomness would be inefficient and dangerous.” For example, cancer can arise when gene expression is allowed to unfold unchecked. Associate Investigator and lead author Julia Zeitlinger, PhD, believes that by understanding the basic mechanisms that control gene expression, researchers can gain a greater appreciation of the underlying causes of cancer and related diseases.

This study was published online May 15, 2017, in Nature Genetics.
When Alice Accorsi, PhD, first encountered the freshwater snail *Pomacea canaliculata*, it was as an invasive pest of crops and the intermediate host of a parasitic roundworm that can cause human encephalitis.

Accorsi, then a graduate student at the University of Modena and Reggio Emilia in Modena, Italy, was searching for vulnerabilities in the snail’s immune system that could be targeted to eradicate the pest.

Today, as a postdoctoral researcher at the Stowers Institute, Accorsi is one of a few scientists worldwide who is studying *P. canaliculata* not as a pest, but as a new laboratory model for research on the molecular and cellular processes responsible for the regeneration of complex eyes.

Like humans, this snail has camera-type eyes that use a single lens to focus images onto the retina. Unlike humans, however, the adult snail can completely regenerate its eyes after they have been damaged or experimentally removed.

Accorsi’s scientific interest in regeneration began at the Marine Biological Laboratory’s 2013 summer embryology course in Woods Hole, Massachusetts. There, she met Stowers Investigator and Howard Hughes Medical Institute (HHMI) Investigator Alejandro Sánchez Alvarado, PhD. A director of the annual course since 2011, Sánchez Alvarado is one of the pioneers in the science of regeneration. A major focus of research in his laboratory has been investigating the role of stem cells in regeneration using the planarian flatworm as a model organism.

Before returning to Italy, Accorsi talked with Sánchez Alvarado about her newfound interest in regeneration and her then current research on the *P. canaliculata* immune system. “Alejandro’s lecture inspired me and made me curious about the potential ability of *P. canaliculata* to regenerate, so when I returned to the lab in Modena, I was able to witness firsthand the snails regenerating some severed body parts over a one-month
period,” she said. Sánchez Alvarado also encouraged her interest in regeneration, and the following year, in 2014, Accorsi spent three months as a researcher in his lab at the Institute.

“The experience helped me define my interests and the scientific questions I would like to answer as a postdoc,” Accorsi says. “It was as if I had discovered a new world!”

A year later, Accorsi returned to the Sánchez Alvarado Lab to conduct her postdoctoral studies on regeneration in *P. canaliculata*. Accorsi hopes to uncover the biological mechanisms that regulate the snail’s embryonic development of eyes and determine whether these mechanisms are similar to those that underlie regeneration in the adult animals. She also plans to determine how a complex organ, such as a camera-type eye, can be rebuilt *de novo* in the adults and how the regenerated eye cells communicate and connect to the preexisting cells in the snail’s nervous system. This research has the potential to lay the groundwork for the discovery of new mechanisms or molecules that might also have an impact on human health, Accorsi says.

In addition to conducting research, Accorsi has been busy with a novel educational project called *The Planarian Educational Resource, Where Cutting Class Is Required*. In collaboration with Sánchez Alvarado and other Stowers and HHMI researchers, Accorsi created the website and published a companion article, “Hands-on classroom activities for exploring regeneration and stem cell biology with planarians,” in the March 2017 issue of *The American Biology Teacher*. Accorsi hopes that the educational activities described on the website will encourage students’ interest in and enthusiasm for science.

Accorsi, who enjoys the music scene and the diverse cuisines of Kansas City, says that she “can’t think of a better place to conduct science than the Stowers Institute. We’re free to think big, and we do!”

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Ruohan Zhong  
_Zhejiang University_  

As a child, Ruohan Zhong wandered the woods and hills around her home. It was during these explorations that her curiosity about nature was born.

Zhong’s early quest to learn about the natural world led to deeper exploration of subjects that intrigued her. Her studies ultimately led to a fascination with epithelial cells and how they develop into organized structures.

Zhong graduated from Zhejiang University in Hangzhou, China, with a BS in agricultural sciences in applied bioscience. There, she focused her research efforts on botany.

Sharien Fitriasari  
_University of Missouri_  

Sharien Fitriasari is no stranger to the long hours required for laboratory research. While working on her BS in biochemistry with a minor in business at the University of Missouri at Columbia (MU), she worked 12 to 15 hours a week in a lab in the MU biochemistry department, focusing on genetic modifications of sulfate-reducing bacteria that would consume toxic metals contaminating the environment. And, in addition to that, she interned two separate summers in Jakarta, Indonesia, with the drug companies Merck and Novartis.

As a life sciences undergraduate intern, experiences examining bacteria-metal interactions solidified her desire to pursue a PhD and a career in research science.
• **Raktim Roy**  
  *Jawaharlal Nehru Centre for Advanced Scientific Research*

Raktim Roy is an ambitious young man inspired by his diverse tastes in science, movies, books, and music. The movies *Jurassic Park* and *Spider-Man* and a biography on Albert Einstein ignited Roy’s early interest in science. Science fiction and the superheroes of books and movies continued to draw his attention to science as a youngster, which in turn led him to pursue a BS in biochemistry from Presidency University in Kolkata, India, followed by an MS in molecular biology and genetics at Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR) in Bangalore.

His studies at JNCASR nurtured his interest in epigenetics and chromatin biology, but a master’s course in transcription and regulation of gene expression is what really captured his scientific attention.

• **Rahul Garg**  
  *Indian Institute of Technology*

Rahul Garg began his path to a career in biomedical research with an introductory undergraduate course in physiology his sophomore year in college. The nervous system’s network and complexities in signal processing particularly intrigued him. After completing a small research project on the olfactory system of *Aedes aegypti*, also known as the yellow fever mosquito, he was hooked.

Garg would like to continue exploring neuroscience and behavioral biology, with the ultimate goal of helping find cures for neurodegenerative diseases by decoding the inner workings of neural circuitry.

• **Kai Zhang**  
  *University of Science and Technology of China*

Kai Zhang first became interested in science during a high school genetics class. He was fascinated with the idea that a single point mutation in DNA could lead to completely different human characteristics. As he studied more, Zhang focused on what he calls the ‘biological magic’ of how animals are systematically structured by their various genes. So, it’s no surprise that Zhang earned his BS in biological science from the University of Science and Technology of China in Hefei with a research specialty in genetics and transcriptional regulation.

Under the tutelage of Stowers mentors, Zhang looks forward to working toward his PhD in world-class facilities with the support and scientific freedom for which the Institute is known.

• **Julia Peloggia**  
  *University of São Paulo*

Failure was not something familiar to Julia Peloggia. Always intrigued by biological science, Peloggia entered the University of São Paulo with the idea of becoming a geneticist. However, after a biochemistry course her freshman year turned out to be more difficult than expected, she realized that she would need to focus her efforts and study harder.

With that early challenge serving as a life lesson and long behind her, Peloggia recently graduated from University of São Paulo, Brazil, with a BS in biological sciences and a desire to pursue a PhD, perhaps in developmental biology and regeneration.

• **Azqa Khan**  
  *Lahore University of Management Sciences*

An early encounter with a cockroach set Azqa Khan on the road to a career in biological science.

It was during a ninth-grade biology class that Khan had to dissect one of the insects. Once she overcame her fear, she recalls being blown away by what she describes as “the magnificence of the cockroach’s design.” Khan studied more organisms, their internal systems and genetics, and grew ever more certain that biological science would be a key focus in her life.

Khan comes to the Institute from Pakistan with her BS in applied biosciences from the National University of Sciences and Technology, and her MS in biology from Syed Babar Ali School of Science and Engineering at Lahore University of Management Sciences.

• **Paloma I. Meneses Giles**  
  *National Autonomous University of Mexico*

Paloma Meneses Giles first developed a particular interest in cell and developmental biology in high school and was thoroughly hooked after participating in the National Biology Olympiad in Mexico.

Later, as an undergraduate at the National Autonomous University of Mexico (UNAM) in Cuernavaca, she explored the field as she moved among different labs and became captivated by the nature of stem cells and the complexity of cancer biology.

In 2014, while still an undergraduate, Meneses joined the lab of Stowers Investigator Linheng Li, PhD, to work on a one-year project. She later earned her BS in genomic sciences from UNAM.
Todd Bradley, PhD, who conducted his graduate research at the Stowers Institute from 2007 to 2013 while studying for his doctoral degree at the University of Kansas (KU) School of Medicine, is playing a key role in Duke University’s efforts to design a vaccine that will prove more effective than currently available experimental vaccine regimens in protecting people against HIV-1, the virus that causes AIDS.

Bradley, who received his PhD in pathology and laboratory medicine in 2013, is director of the Duke Human Vaccine Institute Viral Genetic Analysis core facility in Durham, North Carolina. He was appointed to this position in 2016 after completing a three-year postdoctoral research fellowship at Duke. “I study the good and bad parts of the body’s immune response to vaccines and infections,” Bradley says. “This information helps in the design of more effective vaccines.”

His research has been very productive. Since 2016, Bradley has coauthored 10 scientific papers including a widely publicized Nature Communications article published in June 2017 detailing a new HIV-1 vaccine strategy.

To improve the HIV-1 vaccine, the Duke-led research team took an innovative high-risk, high-reward approach, a type of approach valued by the Stowers Institute, Bradley says. “One of the reasons that I enjoyed working at the Institute is its support for scientists who investigate the most important research questions even though they could be very difficult to solve,” says Bradley, who conducted his graduate studies on the basic mechanisms of RNA processing in the lab of former Stowers Investigator Marco Blanchette, PhD.

While an undergraduate at KU, Bradley worked part-time as a research assistant in the lab of a basic biomedical scientist who had developed a mouse model of the immune system in systemic lupus erythematosus, commonly called lupus. He also volunteered at the University of Kansas Hospital. “Because I was finding the research lab more intriguing than the patient care setting, I began wondering if my next step should be studying for a PhD rather than an MD,” he says. “I didn’t realize that I could do both—be a physician who takes care of patients and makes scientific discoveries.”

“Before applying for a PhD program, I wanted to be sure that I could be devoted to full-time bench work,” he reveals. Thus, after graduating with his BS degree, he worked full-time for one year as a research technician in Blanchette’s lab at the Stowers Institute. The experience convinced him to study for a PhD—and return to the Institute to perform his graduate research.

When young researchers ask about the Stowers Institute, Bradley describes its cutting-edge technology, collaborative approach to science, and its support of high risk, high-reward research. “The Institute is small enough to have a real sense of community. And, because of its diverse research and relatively small size, young researchers are exposed to a wide range of research areas,” he explains.

Until recently, Bradley’s life had not changed significantly with the move from Kansas City to Durham. He has continued to be passionate about his research and to relax by hiking, cooking new recipes, and binge-watching new Netflix series. However, a recent development has upended his and his wife Elyse’s schedules. On July 2, their first child, a boy named Lucca, was born. 😊
Kulesa scores NIH grant to study neural crest cell migration

Stowers Director of Imaging Paul Kulesa, PhD, has received a two-year grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health to study how microenvironmental signals sculpt cells into distinct migratory streams.

Cranial neural crest cells must travel from their neural tube origin to target locations in the developing head where they give rise to bone, cartilage, neurons, and glia. In order for facial structures to form in the proper order, neural crest cell invasion must be controlled so that migrating cells form and remain in segregated streams.

Kulesa and Rebecca McLennan, PhD, a research scientist in the laboratory, plan to utilize state-of-the-art techniques, including time-lapse microscopy, to examine gene expression patterns and cell behaviors. Knowledge of the factors that control neural crest cell migration will help us better understand craniofacial birth defects and be relevant to highly aggressive neural crest-derived cancers, such as melanoma.

Jaspersen awarded multiyear NIH grant

Associate Investigator Sue Jaspersen, PhD, has received a grant from the National Institute of General Medical Sciences of the National Institutes of Health to examine the assembly and regulation of yeast spindle poles. When yeast cells divide, spindles are required for the equal partitioning of genetic material in the form of chromosomes to the daughter cells.

Errors in the formation of spindles are associated with a loss or a gain in chromosome number, which can lead to an increased risk for cancer and birth defects. Jaspersen and her team will probe the mechanisms involved in the assembly of spindles.

By using innovative imaging techniques that provide unprecedented resolution combined with genetic and molecular methods, they hope to determine the mechanisms involved in the spindle pole body cycle of duplication and DNA replication.

Baumann takes von Humboldt Professorship in Germany

Howard Hughes Medical Institute and Stowers Investigator Peter Baumann, PhD, was awarded a prestigious Alexander von Humboldt Professorship. The professorship comes with a 5 million euro award for those conducting experimental research and was created to support the recruitment of established researchers to German universities.

According to the Humboldt Foundation, which awards the prize, about half of the candidates, like Baumann, are Germans returning from abroad.

Baumann joined the Stowers Institute in 2002. His lab studies various aspects of chromosome biology ranging from the maintenance of chromosome ends by telomerase to the effects of hybridization, ploidy changes, and unisexual reproduction in the context of evolution. He plans to leave the Institute in 2018 to join the Institute of Molecular Biology at the University of Mainz, Germany.
Scientists in training earn competitive funding awards

Postdoc to study cell fate and signaling with three-year fellowship

During development, special signaling centers within an organism instruct the growth and differentiation of neighboring cells and establish patterns critical to the formation of adult organ systems. In adult organisms, regeneration of damaged organs and abnormal growth of diseased tissues (tumors) also require the formation of signaling regions that induce growth and differentiation in nearby cells, but less is known about these processes in adult tissues.

With a highly competitive three-year fellowship grant from the Jane Coffin Childs Memorial Fund for Medical Research, Blair Benham-Pyle, PhD, will focus her research efforts on identifying the cell types and signaling patterns required for adult tissue regeneration as well as the unique signaling molecules and cellular interactions that are required for successful tissue patterning and organization.

Benham-Pyle, a postdoc in the Sánchez Alvarado Lab, will undertake her research in planarian worms because they provide a unique opportunity to study organizing activity in adult tissues due to their extraordinary ability to regenerate entire organ systems from tiny tissue fragments.

Benham-Pyle anticipates that her work will shed light on mechanisms underlying the remodeling and self-assembly of adult tissues, which could advance the fields of cancer biology and regenerative medicine.
Studies proposed to further understand a cancer treatment secure postdoc a fellowship

SAHA is an FDA-approved chemotherapeutic agent that has found success as a treatment for T-cell lymphoma. This histone deacetylase (HDAC) inhibitor is part of over 240 past or ongoing clinical trials that seek to examine SAHA efficacy as a treatment option for many other cancers. Yet despite widespread study at the clinical level, the therapeutic potential of SAHA and other HDAC inhibitors is hampered by a rudimentary understanding of the molecular mechanisms that mediate their actions.

Mark Adams, PhD, a postdoctoral research associate in the Washburn Lab, has won fellowship funding from the National Institutes of Health for studies that may shed light upon these mechanisms and characterize the response of the SIN3 HDAC complexes to SAHA.

Because SAHA and other HDAC inhibitors are already components of clinical treatment plans, this research has the potential to produce information immediately relevant to therapeutic use. Longer term, these findings may provide the groundwork for the development of HDAC inhibitors that target specific aspects of HDAC complexes and produce fewer side effects.

Early Independence Award goes to Stowers postdoc

Chuankai Zhou, PhD, joined the company of other exceptional young scientists when he was selected as a 2017 NIH Director’s Early Independence awardee. The five-year award supports outstanding junior scientists who demonstrate the intellect, scientific creativity, drive, and maturity needed to flourish independently and allows an opportunity to bypass the traditional postdoctoral training period. It is designed to travel with the researcher to an independent research position.

Zhou, who was a postdoc in the Kausik Si Lab, recently began a position at the Buck Institute for Research on Aging in Novato, California. There, he continues to study the factors that underlie aging, specifically what happens when a process called proteostasis, which helps maintain a healthy balance of proteins within a cell, is disrupted and aggregated proteins accumulate. Zhou anticipates this work will advance the understanding of aging and age-related diseases that involve proteostasis, thereby establishing a basis for future explorations of rejuvenating aged cells and developing interventions for age-related diseases.
In July, Stowers Associate Investigator Julia Zeitlinger, PhD, co-organized an American Society for Biochemistry and Molecular Biology (ASBMB) Special Symposium at the Stowers Institute. This international meeting brought some of the brightest scientific minds to Kansas City for a four-day meeting focused on evolution and core processes in gene expression. More than fifty speakers from a variety of research institutions presented their scientific data and inspired a wide range of discussion topics.

“Hosting this kind of gathering serves several purposes,” shares Zeitlinger. “Beyond the opportunities it offers to advance a scientific dialogue, it showcases the Stowers Institute and the amazing facilities we have, and it further promotes Kansas City as an established yet growing hub for the biosciences.”
Members of the Jerry Workman Lab organized a scientific symposium to mark 25 years of his lab leadership. Many former lab members traveled from around the world to attend the celebration.

Similarly, current and former lab members of Stowers Scientific Director Robb Krumlauf organized a symposium to commemorate his many years of mentorship and his recent induction into the National Academy of Sciences.

This fall the Institute hosted celebration events for two Stowers investigators.
Incoming, outgoing, delivery, pickup, first-class, priority, registered, certified, bulk, international. With a dizzying array of shipping, mailing, and delivery options, the Stowers Receiving Center expertly manages the critical lifeline of supplies and print mail flowing into and out of the Institute.

Not only does the team receive and deliver the constant supply of scientific paraphernalia and equipment, they assist Stowers laboratories with special deliveries and international shipments that allow scientific samples and reagents to be shipped around the world.
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TO MAKE A SIGNIFICANT CONTRIBUTION TO HUMANITY THROUGH MEDICAL RESEARCH BY EXPANDING OUR UNDERSTANDING OF THE SECRETS OF LIFE AND BY IMPROVING LIFE’S QUALITY THROUGH INNOVATIVE APPROACHES TO THE CAUSES, TREATMENT, AND PREVENTION OF DISEASES.

Neural crest cells are a group of embryonic cells that migrate to various locations in the body where they give rise to different cell types and contribute to the formation of tissues and organs as an embryo develops. This image shows a cross section through the central nervous system of a mouse embryo. Neural crest cells, which make bone, cartilage, neurons, glia and other cell types throughout the body, are labeled in green, whereas microtubules, which are structural components of cells, are labeled in red. Cell nuclei are labeled in blue.

Image courtesy of Annita Achilleos, PhD, Trainor Lab.