STOWERS INSTITUTE®
FOR MEDICAL RESEARCH

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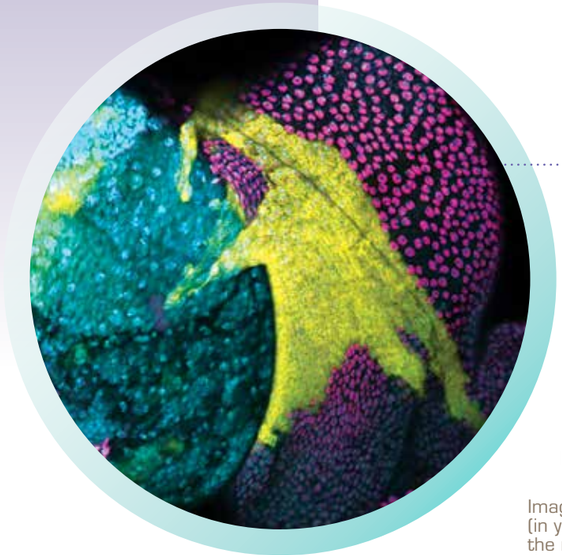
OUR MISSION:

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.



THE GENETIC CODE STORED IN DNA IS INTERPRETED DURING GENE EXPRESSION WHICH, ALONG WITH THE ENVIRONMENT, SHAPES AN ORGANISM'S PHENOTYPE – ITS OBSERVABLE TRAITS. INVESTIGATOR JERRY WORKMAN'S RESEARCH FOCUSES PRIMARILY ON UNDERSTANDING THE FIRST STEP IN GENE EXPRESSION WHERE DNA GETS COPIED TO RNA AND DETERMINING WHAT MOLECULES MODIFY THIS PROCESS.

Image: The larval eye of a fruit fly showing a subset of cells (in yellow) lacking an enzyme called Enok, which assists in the regulation of gene expression. Cells that lack Enok show decreased levels of a gene expression marker (pink). Cell nuclei are shown in blue.

LAMPREYS, CAVEFISH, FLATWORMS, & SEA ANEMONES, OH MY! AMASSING A MENAGERIE OF EMERGING MODEL ORGANISMS.

STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH FALL/WINTER 2015

STOWERS REPORT

PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH
FALL/WINTER 2015

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The Stowers Report is published by the Science Communications Department at the Stowers Institute for Medical Research. We welcome your input. Please send comments to communications@stowers.org or contact us at (816) 926-4015.

In perspective

BY DAVID CHAO, PHD
PRESIDENT AND CEO

Over the decades, model organisms such as yeast, fruit flies, and mice have allowed researchers to answer countless questions about biological processes. More recently, technological advances have expanded the number of model organisms available for basic biomedical research.

On a typical day at the Stowers Institute, one might find a half-dozen researchers sitting at a row of microscopes, inspecting immobilized fruit flies and sorting the female from the male, the red-eyed from the white-eyed, or the winged from the wingless. Known informally as "fly pushing," this activity is a key part of the genetic screens essential for fruit fly research.

The core essentials of fly pushing – fruit flies, microscopes, small brushes and researchers – are the same as they were one hundred years ago in Nobel Laureate Thomas Hunt Morgan's famous fly room at Columbia University. Morgan was instrumental in popularizing the fruit fly as a model system to understand how inherited factors are passed down through generations. As demonstrated at the Institute by the Gibson, Hawley, Si, Xie, Workman, and Zeitlinger laboratories, the fruit fly continues to have a prominent place in modern biological research.

Many researchers choose to study processes in the fruit fly because its devotees can draw upon a century's worth of data, insights, and research tools. The fruit fly is one of a handful of species that are well-recognized and well-studied standards called "model organisms". For centuries, biologists studied thousands of different species, without any one species achieving critical mass and establishing itself as a standard. The fruit fly was one of the first species to achieve critical mass, followed by other species including the gut bacteria, *Escherichia coli;* a bacterial virus called phage; baker's yeast; the roundworm; zebrafish; and mice.

Each of these model organisms is particularly well suited to address questions in a specific area of biology. However, the availability of only a handful of organisms leaves many gaps unaddressed. Fortunately, recent technological advances have reduced the time and effort needed to sequence, compare, annotate, and manipulate new genomes, and help fill the gaps.

This issue's cover story describes several emerging model systems used in the Institute's research programs. Stowers investigators are able to pursue these programs because of superlative support from the Institute's scientific support facilities. The Laboratory Animal Support Facility, Reptiles and Aquatics Facility, Computational Biology Core, Research Advisors, and Molecular Biology Core all accelerate the development of new model organisms by applying their expertise in areas like animal husbandry, genome analysis, and genome manipulation.

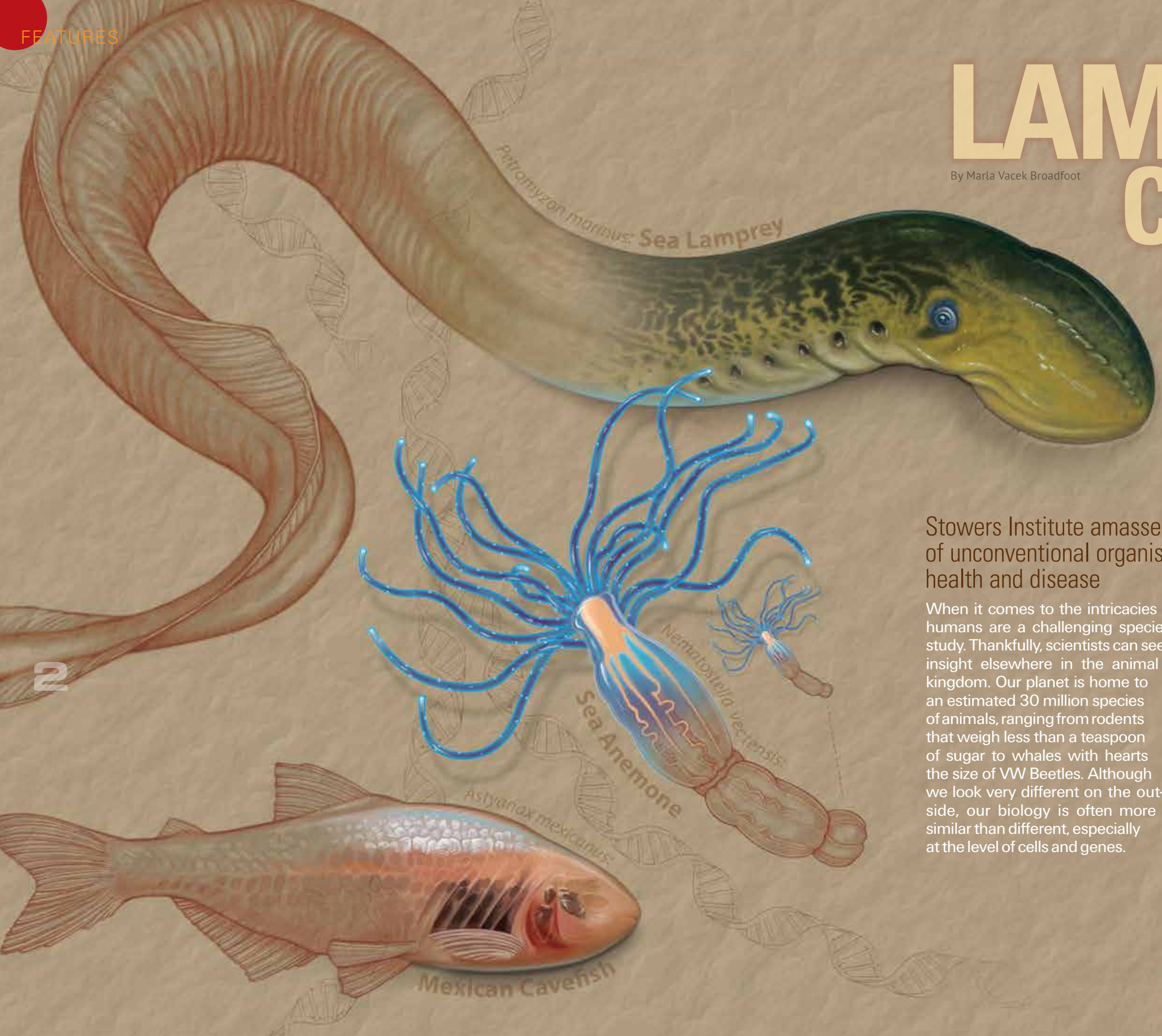
Part of Jim and Virginia Stowers' vision for the Institute has been to enable its members to pursue research that is difficult or impossible anywhere else. Streamlining the process by which investigators can develop and study new model organisms is but one example of how the Institute is seeking to achieve their vision. I hope you enjoy reading about emerging model organisms and other innovative projects in this issue of the Stowers Report.

LAMPREYS, CAVEFISH, FLATWORMS, & SEA ANEMONES, OH MY!

By Marla Vacek Broadfoot

Stowers Institute amasses menagerie of unconventional organisms to study health and disease

When it comes to the intricacies of biology, humans are a challenging species to study. Thankfully, scientists can seek insight elsewhere in the animal kingdom. Our planet is home to an estimated 30 million species of animals, ranging from rodents that weigh less than a teaspoon of sugar to whales with hearts the size of VW Beetles. Although we look very different on the outside, our biology is often more similar than different, especially at the level of cells and genes.



Over many decades, biologists have brought several of these organisms into their laboratories, assembling aquariums for striped zebrafish or vials to house skittering fruit flies. However, they have mostly stuck with a small handful of animal models, favored because they are easy to domesticate or are simple to breed in large numbers.

Robb Krumlauf, PhD, thinks it is time to branch out. As scientific director of the Stowers Institute, he is not surprised that Stowers investigators are amassing a menagerie of emerging model organisms, including bloodsucking lamprey eels, blind cavefish, self-regenerating flatworms, and fluorescent sea anemones.

"The ability to mine the diversity of nature in a mechanistic way is a real strength of modern biology," says Krumlauf. "Our philosophy is to use the latest molecular tools to ask specific questions about the unique way other organisms do things, and to discover new biology that will hopefully be important for understanding human disease," says Krumlauf.

"The ability to mine the diversity of nature in a mechanistic way is a real strength of modern biology."

Bloodsucking lamprey eels

Krumlauf knows a bit about developing model organisms. As a young scientist in the 1980's, he was among the first to insert genes into the mouse genome to create "transgenic" mice that mimic human development and disease. Since then, he has used these mouse models to study how vertebrates like mice and humans evolved their unique features. His work in mice has shown that a set of genes, called Hox genes, control the layout of a developing embryo, marking where structures should appear along the bodyplan from head to tail. This sort of molecular ruler is present not only in mice and humans, but also at play in more primitive organisms, from flies, to worms, to fish.

Further down the tree of life, back 500 million years to the base of the vertebrate branch, lies one of the most unappealing animals in existence, the sea lamprey *Petromyzon marinus*. These long, eel-like fish use a jawless mouth armed with spiraling rows of horny teeth to latch on to their prey and feed. Researchers had assumed lamprey lacked jaws because their Hox genes weren't operating the same way as they were in higher vertebrates. Krumlauf thought this jawlessness might be due to the activity of Hox genes in a specialized brain structure called the hindbrain, which coordinates basic functions like heartbeat, breathing, and jaw movement. But testing this theory meant Krumlauf would have to get his hands on these bloodsucking creatures.

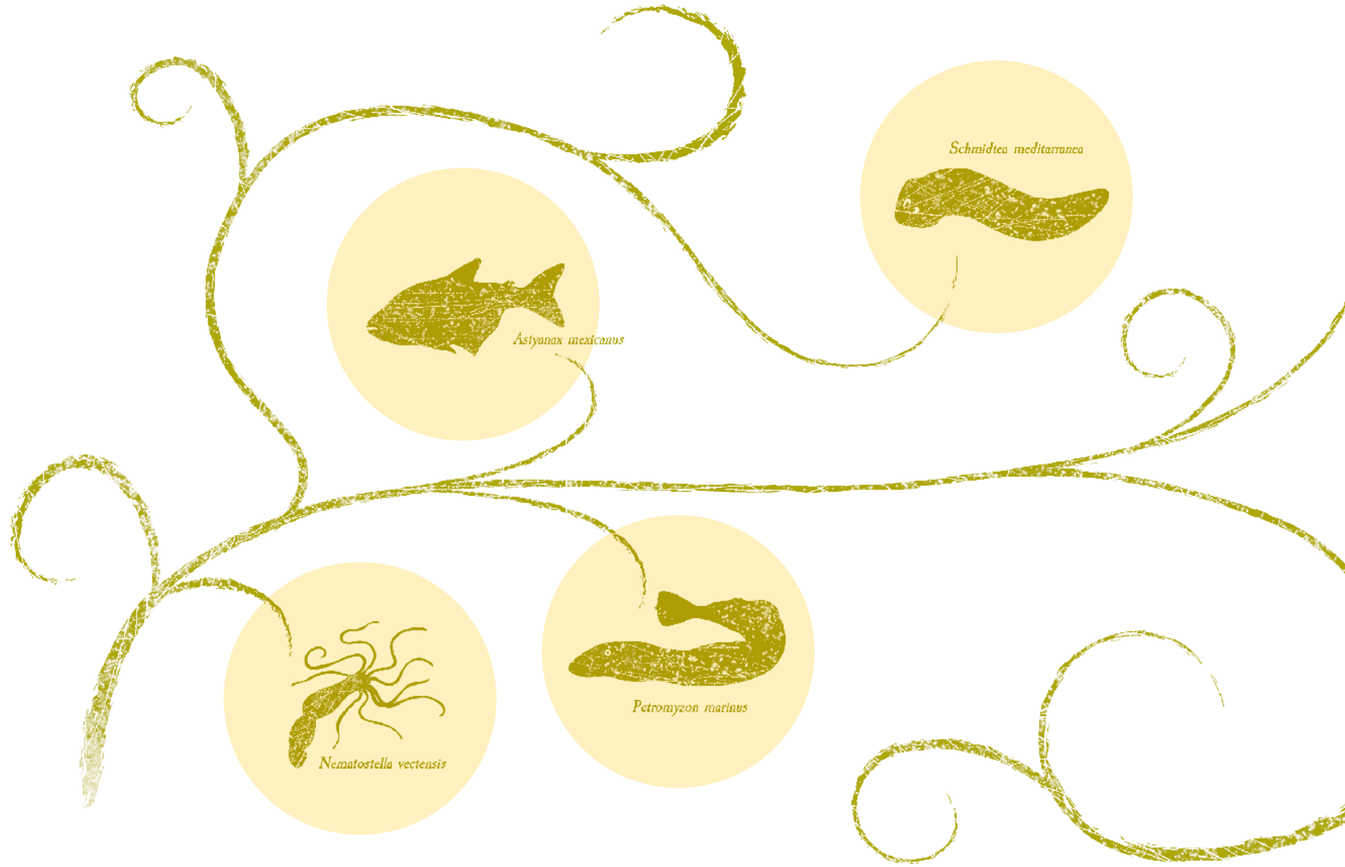
Though lamprey are difficult to study in captivity, there are plenty of these parasitic fish in the sea. Just like adult salmon return to the spawning ground of their birth, lamprey swim from the ocean to freshwater streams and lakes to spawn and lay their eggs. Every summer, Krumlauf's collaborator, Marianne Bronner, PhD, obtains egg-bearing lampreys out of the waters of the Great Lakes and sets them up in tanks at CalTech, where the slimy sea creatures churn out tens of thousands of fertilized eggs. At the same time, Stowers researchers migrate from Kansas City to California each summer to study the resulting embryos—tiny translucent spheres that belie their horny-toothed parentage.

"I don't think any of us would look forward to studying this animal if we had to work with the full grown organisms all the time. Lamprey are the ugliest beasts you can possibly imagine. But the embryos are really striking and beautiful," says Krumlauf.

During one of these trips, a member of Krumlauf's team, Hugo Parker, PhD, manipulated these tiny embryos by attaching fluorescent tags to the molecular switches that turn the Hox genes on or off. They then placed each embryo under a fluorescence microscope and watched the light show unfold as the organism began to develop towards its adult form. To their surprise, the molecular switches in the hindbrain lit up exactly the same way in jawless lamprey as they did in jawed vertebrates like zebrafish. So how could the same genes give rise to such strikingly different animals?

"We think it may be like going to the hardware store, where you can buy the same building materials but you can build a lot of different kinds of structures with the same tools and materials," says Krumlauf. "The ancestral function of the original genes might be the same, but these organisms have evolved different functions over the years."

Now, the Krumlauf team is studying the mechanisms driving this evolutionary process, which they hope will give insight into how these instructions are used in humans and how they can get misinterpreted in disease.



Blind cavefish

Unlike the lamprey, which has a face only a mother (or dedicated scientist) could love, the cavefish *Astyanax mexicanus* is a popular aquarium oddity. These creatures not only lack eyes but are also completely devoid of pigment, giving their bodies an almost ghostly pinkish-white sheen. Cavefish are more than just a funny-looking pet – they are the product of evolutionary forces at their most brutal and unforgiving.

In the wild, these cave dwellers must survive in pitch-black surroundings, where the only food available is swept into the caves once a year when rivers flood. Along with animal and plant remains, the floods also bring in fresh recruits of surface fish from nearby waters that must also adapt to their harsh new environment, or die trying. Over time, the gene pool of the survivors evolves as they shed seemingly pointless properties, like eyesight and coloring, and acquire vitally important ones, like starvation resistance.

Assistant Investigator Nicolas Rohner, PhD, studies this case of extreme evolution, and has found cavefish remain startlingly healthy despite enduring repeated cycles of feast or famine. When floods finally deliver their annual meal, the ravenous cavefish gorge themselves until all the food is gone. By the time they are done eating, many of their organs have doubled in size and

they have become ten times fatter than their surface counterparts. Yet these fleshy fish are not prone to any of the obesity-related conditions that plague humans.

"They are a great model for understanding why we as a species store so much fat," says Rohner, who recently completed a postdoc at Harvard and launched his own laboratory at the Institute. "The typical human has about 25 percent body fat; our closest living ape relatives have much less than one percent. From an evolutionary perspective, humans carry a significant amount of body fat, and with modern diets, it's only increasing. It is important to understand why humans are prone to obesity or why we develop illnesses like diabetes and heart disease."

As a postdoc, Rohner maintained tanks full of fat-filled cavefish and svelter, albeit more mundane-looking, surface fish. By breeding the two types of fish with each other, he could follow the inheritance of various traits across generations, much like Gregor Mendel did with his famed pea plants. Rohner combined this classical genetic approach with modern sequencing technology to pinpoint regions of the genome associated with feeding behaviors and appetite. He found cavefish have a mutation in melanocortin 4 receptor, or MC4R, a gene known to give people an insatiable appetite when mutated. It is the most common single genetic cause of obesity.

Now that he is at the Stowers Institute, Rohner and his team will be looking for mutations to explain why cavefish are able to store so much fat without suffering the negative consequences. Such knowledge could lead to new treatments to buffer the effects of metabolic diseases.

"The link between evolution and medicine is undeniable," says Rohner. "Diseases have an evolutionary underpinning, so understanding why we are the way we are could help us to find new approaches to address our weaknesses."

Self-regenerating flatworms

For researchers like Rohner and Krumlauf, tapping the animal repertoire outside of typical lab models allows them to study specific characteristics in their most extreme, exaggerated forms. Gluttonous cavefish become the perfect animal for examining human metabolism. Jawless lamprey present an excellent model for investigating the complexities of brain and head development. Likewise, the self-regenerating flatworm embodies the ideal system for understanding how some organisms regrow damaged organs or missing body parts.

"The technological powers in biology are unprecedented – in a matter of days you can literally go from knowing nothing about an organism to having a comprehensive list of all of the genes that are turned on or off," says Investigator Alejandro Sánchez Alvarado, PhD. "We are witnessing the future of biomedical research, where advances like sequencing and genome editing mean we are no longer constrained to domesticated animals but can look elsewhere in nature to answer questions about disease, aging, and regeneration."

Sánchez Alvarado believes regeneration is one of the last untamed frontiers of developmental biology. Despite decades of research, scientists still don't understand how a few lucky members of the animal kingdom manage to perform this amazing feat. Salamanders can grow back a pinched tail; zebrafish can regrow fins or even chunks of damaged heart tissue. One of the most talented of these regenerative magicians, planaria, can grow an entirely new head after being decapitated. Cutting these miniscule, arrow-shaped flatworms into pieces results in a growing brood of full-sized clones.

Twenty years ago, Sánchez Alvarado began reading up on these resilient creatures, eager to learn their secrets. When he learned that the planaria *Schmidtea mediterranea*, which possesses a small genome size and a small number of chromosomes, could be obtained from an abandoned fountain in a park in Barcelona, he and his then post-doctoral fellow Phil Newmark, PhD, flew to the city and set liver-baited traps in every fountain they could find. The researchers then turned their catches into a line of hundreds of thousands of planaria that are now being used in laboratories all across the United States.

In Sánchez Alvarado's own laboratory, his team is creating a genetic flow chart to describe how this miraculous process unfolds in planaria. First, they take a razor blade to the animal, cutting off a head or vital organ like the pharynx. Then they measure how the worm's more than 20,000 genes are turned on or off as they begin to grow back pieces of flesh. Once the researchers know which genes are at play, they use advanced molecular techniques like RNA interference to silence each of these genes to see how it affects the animal's ability to regenerate the next time it goes under the knife.

Thus far, his team of scientists has identified several groups of genes responsible for successful regeneration. Some, like a gene called ß-catenin, help the organism figure out whether it needs to grow back a head or a tail. Others, including the gene FoxA, are in charge of rebuilding a specific organ. Ultimately, each disfigured planaria is made whole again through the action of stem cells, the same cellular entities responsible for replenishing dead or damaged cells that course through our veins, line our gut, and cover our skin.

"If we could glean information about conserved mechanisms between worms and humans, we could understand why we can only use these same cells to repair simple wear-and-tear and not to launch a full-blown regenerative response," says Sánchez Alvarado.

Unfortunately, nobody knows whether regeneration is an ability other organisms evolved separately or if it is something that the human lineage once had and lost. To answer that question, researchers will have to examine closely our evolutionary ancestors to find clues for potential human self-healing.

Fluorescent sea anemones

Analyzing the genetic underpinnings of a wide variety of animal species is getting easier as sequencing becomes cheaper and more routine. At last count, the genomes of nearly 2,500 multicellular organisms had been sequenced, including sea lampreys, cavefish, planaria, and sea anemones. These projects have given some unexpected surprises. Take the starlet sea anemone, *Nematostella vectensis*, a seemingly primitive animal that shares a phylum with other simpletons like corals and jellyfish. Unexpectedly, its genome was found to be large and complex, sharing more in common with humans and other vertebrates than traditional model organisms like fruit flies or roundworms.

"Part of gaining access to new knowledge is studying unconventional animal models."

This incongruous finding attracted the attention of Associate Investigator Matthew Gibson, PhD, who has spent most of his career studying development in the fruit fly. Gibson is interested in how animal cells become stacked into highly organized layers called epithelia. These epithelial sheets line almost all body surfaces, constructing barriers for body walls, tissues, and organs. *Nematostella* turned out to be a stunning example of this type of cellular organization, an organism Gibson describes as a "beautiful bag of epithelium."

Close up the sea anemone is strikingly beautiful, a translucent, fluid-filled stem that is crowned with over a dozen delicate tentacles like the petals on a flower. But the organism is hardier than it looks. It doesn't seem to die of natural causes, and will even survive being cut in two by regenerating its other half. When Gibson and his team first viewed these sea anemones under a fluorescence microscope, they noticed glowing patches of bright red color just below the animal's tentacles. Out of curiosity, they cloned the party responsible for the mysterious red fluorescence, a gene later named *NvFP-7R*.

Researchers don't know exactly what purpose *NvFP-7R* serves in sea anemone, though some think it might act as a sort of sunscreen that protects the organism from harmful rays. Gibson and colleagues came up with their own use for the fluorescent protein, as a target for testing two revolutionary genome-editing tools. They used techniques, known as CRISPRs and TALENs, to "knock-out" the *NvFP-7R* gene to erase the animal's bright red patches. Now similar experiments are underway to knock out the genes they are most interested in – those involved in controlling development and the arrangement of epithelial cells.

Epithelial cell biology can provide a valuable window into both normal development and the origins of cancer. Epithelial cells make up the vast majority of human cancers — any diagnosis that carries the word "carcinoma" has epithelial roots, and any cancer that has spread did so by escaping the confines of epithelial sheets. While focusing on fundamental cellular, developmental, and evolutionary problems, Gibson emphasizes the potential significance of this work to cancer research.

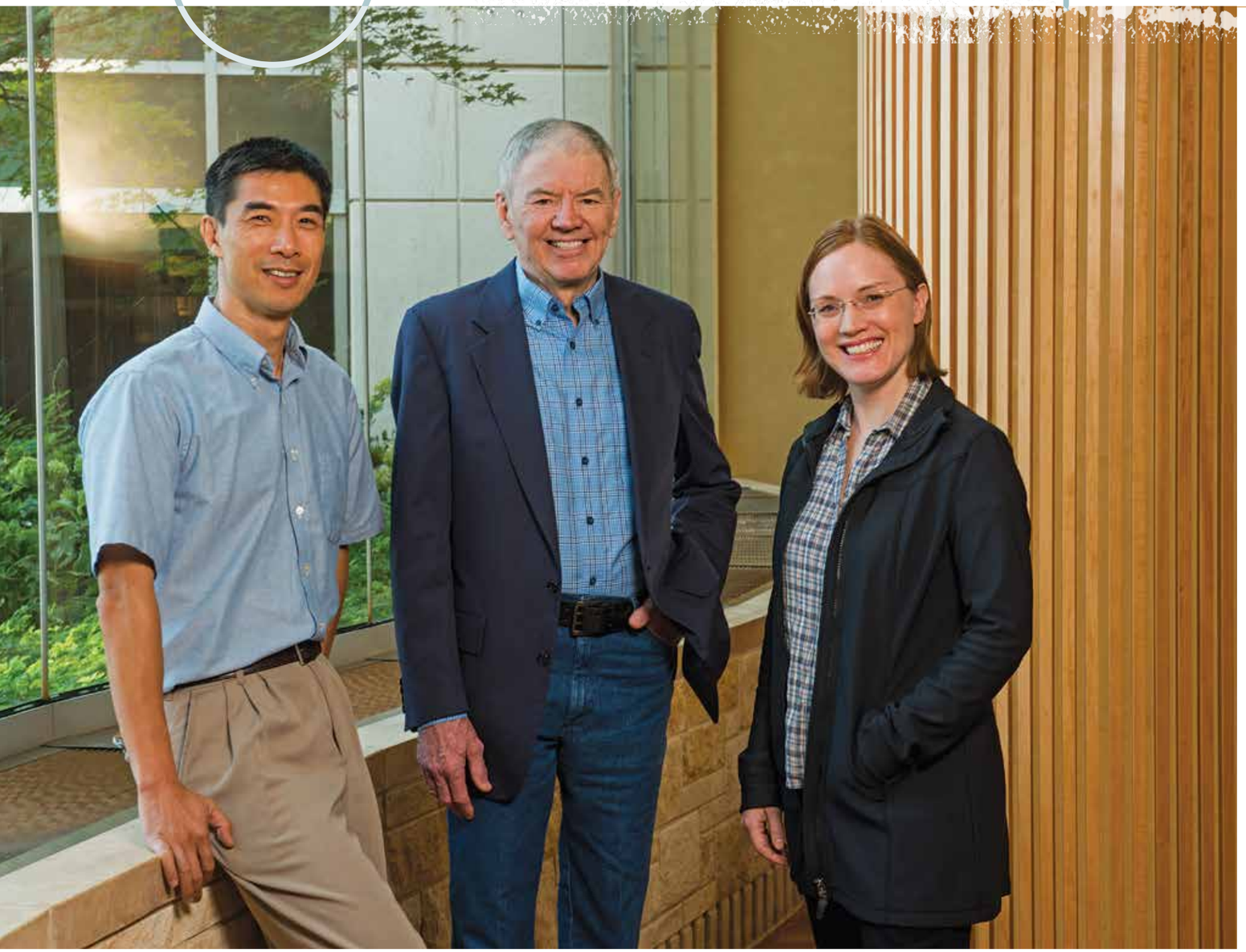
Like other researchers who share company with unusual organisms such as lamprey, cavefish, and flatworms, Gibson is quick to point out that the results with the biggest impact often come from unexpected places. In fact, the CRISPR system of gene editing has revolutionary biomedical implications, yet was originally discovered by researchers studying how bacteria chop up invading viruses. Today it is being used to cut and paste the genomes of many species at will.

"It is a mistake to think we already know everything there is to know because we have looked at a handful of lab animals in detail," says Gibson. "One of the best ways to learn as much as we can is to look in places no one has looked before or to try to ask questions no one has asked before. Part of gaining access to new knowledge is studying unconventional animal models."

By Anissa Orr

Off the beaten path

Neaves Award encourages scientific exploration & innovation



In a perfect world geared toward advancing science, researchers would have the resources to explore whatever promising ideas came their way. But the funding process, which often rewards sure things instead of unproven concepts, forces many scientists to put their riskier, and perhaps best, ideas on the backburner.

Thankfully that's not the case for Stowers Associate Investigators Ron Yu, PhD, and Julia Zeitlinger, PhD. Both are recipients of the 2015 Neaves Award, established in honor of William B. Neaves, PhD, president emeritus of the Stowers Institute for Medical Research. The two-year, $150,000 award was launched in 2010 to encourage and support Stowers researchers who wish to pursue innovative, high-risk research projects with the potential for broad impact.

With the award's backing, Yu and Zeitlinger are keeping their most exciting ideas at the forefront and creating groundbreaking new technologies in biomedical research. "This award not only encourages trailblazing thinking, it rewards it," says Stowers Scientific Director Robb Krumlauf, PhD. "Both Ron and Julia have cultivated important scientific research ideas outside of, but related to their main research programs. The Neaves Award provides critical additional funding to advance these ideas."

Clearer, faster images of the nervous system

Yu's work focuses on the sensory system and identifying the complex connections between neurons that link sensation to behavior. "The mammalian main olfactory and vomeronasal systems give us two ways to look at it," he says.

Yu explains that the olfactory system generally triggers learned behaviors. The smell of freshly-baked chocolate chip cookies evokes happy childhood memories of cooking with a loved one, while the pungent smell of disinfectant calls up unhappy memories of a hospital stay. The triggered memory may influence our behavior (either reaching for a cookie, or fleeing the hospital). The associations we make with smells are often learned, Yu emphasizes.

In contrast, sensory input in the vomeronasal system in mice triggers involuntary or innate behaviors such as the mating process. Yu's 2014 study on this system published in the leading science journal *eLife*, offered new insight into how the mammalian brain processed pheromones to elicit courtship behaviors

Yu will use the Neaves Award to develop a new tool that adds compressed sensing technology to microscopes, enabling rapid imaging of neuronal circuits in the brain. "The idea is to create a device that allows a microscope with the same number of sensors to pick up more signals from our biological sample to increase either the resolution of the image or the speed of acquisition," Yu says. If successful, he expects this tool to become a fully integral part of microscopy systems. Yu plans to use the technology to image the entire mouse brain and trace its neurocircuitry.

Currently, Yu and his team are working on a prototype using software developed by Dar Dahlen, a bioinformatician formerly in the lab. Enlisting scientific advisors and collaborators inside and outside of the Institute, Yu's team will test and implement several designs of the tool's hardware component, which could be attached to a microscope to improve resolution. The funds will also allow Yu to hire another research associate dedicated to the project.

Yu says he never imagined when he joined the Institute in 2004 that he would one day help create a new type of microscopy technology, but the Neaves Award has helped him step out of his comfort zone to pursue research wherever it takes him.

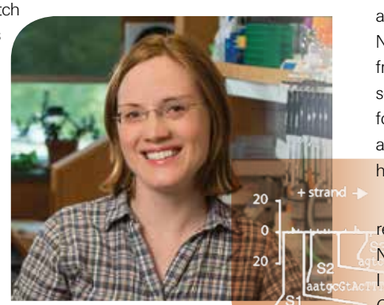
"I don't think this project would have been approved by traditional funding mechanisms," he says. "With the Neaves Award, we have the freedom to explore."

Innovative improvements in DNA mapping

The desire to uncover the rules that govern gene regulation drives Zeitlinger's research, and has been her passion since she joined the Institute in 2007. By investigating the general principles behind gene regulation, Zeitlinger hopes to gain insight that can be applied to the human genome in development and disease.

Gene regulation is the process by which a cell determines which genes to turn on and off and when to create specific cells in the body, for example, a neuron, a brain cell, or the cells that make up skin or bone.

This process usually happens during transcription, when the information in a gene's DNA is transcribed or transferred to RNA, and involves proteins called transcription factors. Transcription factors bind to specific spots in the DNA to switch on and off certain genes. Researchers know that these binding sites are important, but still have trouble finding their exact location.



Determined to zero in on these areas, Zeitlinger and her team developed innovative improvements to a technique called ChIP-seq, which gives investigators an accurate high-resolution map of transcription binding sites.

She and colleagues Qiye He, PhD, and Jeff Johnston published their first paper on the improved technique, called ChIP-nexus, in the April 2015 issue of *Nature Biotechnology*. ChIP-nexus is already yielding new information, showing that binding factors are not scattered across the genome as previously thought, but rather appear in specific, predictable sequences.

Now Zeitlinger is using the Neaves Award to make further tweaks to ChIP-seq technology that will allow researchers to analyze transcription factor binding in populations of cells too small to be characterized by previous technologies. Zeitlinger believes the resulting novel technique, deemed ChIP-next, could be a game changer for genetic researchers, particularly those who prefer to work with cells from intact tissue, which can be limited in quantity, instead of more abundant cultured cells.

Intact tissue cells are often preferred over cultured cells because they can be examined in their natural context. However, using current technologies, a vast amount of live cells—sometimes numbering in the millions—need to be collected per experiment to provide an accurate picture of the genome. "If you want to study gene regulation in real organisms, from embryos or specific tissues in the body, you don't have that many cells available," Zeitlinger says. "ChIP-next is ideal for researchers investigating a specific stem cell niche or a particular system in the body."

With funds from the Neaves Award, she plans to implement ChIP-next and add another researcher to the project. Zeitlinger credits the award for continuing the project's momentum.

"If this technology can be used for much more specific cell types, then it could be attractive to many scientists and a great deal of regulatory information could be collected over time. This would have a huge impact on the field," Zeitlinger says, adding that the technique also holds promise for human health. At the moment, linking genes with particular developmental defects is difficult at best. "But, having all this information will make it much easier to make associations between a developmental defect and what went off course genetically."

Continuing the legacy of Dr. William B. Neaves

Both researchers' projects exemplify the type of innovative research the Neaves award was established to support, says the award's namesake, William (Bill) B. Neaves, PhD. Neaves served as Stowers' President and CEO from 2000 to 2010, recruiting world-class scientists to the then-fledgling institution and fostering an environment where researchers and their work flourished. He's happy to see his legacy continue with the Neaves Award.

"I cherish my association with the outstanding research programs of Ron Yu and Julia Zeitlinger," Neaves says. "Together with Robb Krumlauf, I had the privilege of recruiting Ron from Columbia University and Julia from Massachusetts Institute of Technology. Now that each of them has received the award established by the Stowers Institute in my name, I feel doubly honored."

Stowers President and CEO Dave Chao, PhD, explains that Neaves played an invaluable role in creating an environment that encourages its researchers to pursue challenging questions with novel and creative approaches. "For more than a decade, Bill has always embodied and fostered a pioneering spirit at the Institute," he says, "An award enabling Stowers investigators to pursue creative and ambitious work in new areas is aptly named to honor Bill."

By Patrick Regan

An inspiring journey — Bill Neaves' lifelong study of reptiles

Leaning forward, fixing his eyes on a seven-inch lizard skittering across the sand at the bottom of a blue kiddie pool, Stowers President Emeritus William (Bill) Neaves, PhD, asks, "So, this is *neotigris*?" The lab tech at the Stowers Institute's reptile facility confirms his presumption. "That's a male *tigris* crossed with an all-female species, *neomexicanus*," Neaves declares with unabashed excitement. "What striking animals. I need to come back and take some photos."

The colony of 800 whiptail lizards at the Stowers Reptile & Aquatics Facility is one that Neaves could only have dreamed of when he began his research career nearly fifty years ago. His boyhood fascination with lizards never abated, and as a young man his interest came to focus on several species of whiptail lizards native to the American Southwest and northern Mexico. So strong was that interest, in fact, that it would reset the course of Neaves' career.

Having earned an undergraduate degree in biology, Neaves began medical school at Harvard in 1966 with the notion of eventually returning to his West Texas hometown of Spur to practice medicine. By the mid-1960s papers appeared reporting the unusual chromosomal characteristics of certain whiptail species. Neaves had first learned of the high probability of an all-female species while working as a National Science Foundation summer fellow in the Chihuahuan Desert in 1964. He was determined to know more.

In the summer of 1967, he and his young wife, Priscilla, packed up their Volkswagen camper van and set out for Alamogordo, NM, to collect lizards. At the end of one long day of collecting, Neaves noticed a lizard with an uncharacteristic intense blue coloration on its tail and abdomen. As analysis would later prove, he had captured a previously unknown hybrid tetraploid, a healthy lizard with four sets of chromosomes.

That autumn, Neaves returned to Harvard, but not medical school. Instead, he began working toward a PhD in anatomy, writing his dissertation on the reproductive biology and evolution of lizards. In 1968, the journal *Science* published Neaves' first lizard-related paper exploring mating between different lizard species and parthenogenesis (unisexual reproduction) among whiptails. A second *Science* paper on gene dosage in triploid lizards followed a year later. In 1971, the journal of Harvard's Museum of Comparative Zoology, *Breviora*, published Neaves' findings on the tetraploid hybrid and his speculation about the genetic mechanism of parthenogenesis.

After a two-year Rockefeller Fellowship as a lecturer in veterinary anatomy at the University of Nairobi, Neaves moved back to Texas as an assistant professor of cell biology at the University of Texas Southwestern Medical Center. In the years that followed, Neaves was drawn into academic administration, first serving as dean of Southwestern's graduate school and later becoming medical school dean, a post that, regrettably, left little time for research.

Back then, Neaves had a dream he kept largely to himself. In his retirement, he imagined resuming his doctoral research — building open-air lizard pens out on the old family homestead and conducting whiptail breeding experiments. In early 2000, Neaves agreed to serve as the founding president and CEO of the Stowers Institute, a decision which made his longstanding dream seem unlikely to be realized.

Standing amidst a sea of blue kiddie pools in the reptile facility, Neaves marvels at his good fortune. The whiptail colony—by far the largest colony in the world—was initially formed in 2003 when Peter Baumann, PhD, now an investigator of both the Stowers Institute and Howard Hughes Medical Institute, decided to pick up where Neaves' work left off decades ago. A 2010 *Nature* paper coauthored with other Stowers colleagues resolved the chromosomal mechanism of parthenogenesis. The following year, a *Proceedings of the National Academy of Sciences* paper reported the successful synthesis of the tetraploid as a self-sustaining lineage.

In December 2014, a report published in *Breviora*—forty-three years after Neaves' own *Breviora* paper detailed his discovery of a tetraploid hybrid in New Mexico—took matters to a logical conclusion. The paper announced and taxonomically described a new species, *Aspidoscelis neavesi*, Neaves' Whiptail Lizard.

A half-century after the whiptail first captured his imagination, Neaves' "lizard adventure" is far from over. He anxiously awaits genome sequencing results with full expectation that they will further unravel the mysteries of these extraordinary and enduringly captivating little creatures.

By Cathy Yarbrough

A DISCUSSION WITH

PAUL TRAINOR, PHD

While a graduate student in his native Australia, Stowers Investigator Paul Trainor, PhD, decided to devote his future scientific career to understanding head and facial development. This area of study appealed to him because the human face is inherently interesting from a development, evolution, disease and social perspective. The face has been described as the organ of emotion. It is intimately connected with our identity of self and conveys so much about our social interactions. Oscar Wilde went so far as to say "a man's face is his autobiography".

Trainor's graduate work and ensuing postdoctoral work focused on building the equivalent of a road map of embryonic head and facial development. His goal was to understand and map where neural crest cells come from, where they go, and how they give rise to a wide range of tissues in the body including the bone and cartilage of the face and skull as well as the peripheral nerves that innervate the gut. Many aspects of vertebrate evolution go hand in hand with changes affecting the head and face, and when the mechanisms that drive craniofacial development go awry, the outcome is often a major birth defect.

Birth defects associated with neural crest cells are collectively known as neurocristopathies and include craniofacial anomalies such as Treacher Collins syndrome (TCS) and gastrointestinal tract malformations such as Hirschsprung Disease (HD). In children with TCS, the cheeks, eyes or jaw are often malformed. Hearing loss and respiratory problems also may affect these patients. In HD, neurons are missing from variable regions of the gastrointestinal tract, resulting in intestinal blockage. Children with TCS and HD typically must undergo one or more surgeries to repair these structural abnormalities, but rarely are these procedures fully corrective.

Trainor's lab investigates the development of neural crest cells in laboratory animals, including mouse and zebrafish. Models of TCS were generated by experimentally altering an animal's *Tcof1* gene, which is mutated in most children with the syndrome. Subsequently, Trainor and his team discovered that neural stem and progenitor cells that are the precursors of neural crest cells begin to die in the embryonic brain and spinal cord before these cells have a chance to migrate and begin building the face and head.

The team also determined that experimentally blocking the actions of another gene – named *p53* – could prevent the death of the precursor cells in the embryonic mouse models of TCS. By silencing the *p53* gene, Trainor and his team enabled the nascent neural crest cells to survive, he explains. As a result, the *Tcof1* mutant mouse embryos with inactivated *p53* genes did not develop craniofacial defects. They also found that *Tcof1* plays a role in the development of HD. In laboratory mouse embryos that expressed about half the normal allotment of *Tcof1* and one other gene *(Pax3)*, fewer neural crest cells migrated out of the brain and spinal cord, and many died en route to the gut.

"Approximately one percent of all live births exhibit a minor or major congenital anomaly," says Trainor. "To have any hope of preventing these congenital disorders, you must understand how they originate at a cellular, genetic, and biochemical level. Our findings indicate that intervening to prevent some neurocristopathies during human embryonic development may be possible."

Trainor, who joined the Stowers Institute in 2001 is regarded as a leader in the field of developmental biology by his peers in the international scientific community. He has served as editor for two books on neural crest cells, chaired the 2010 Gordon Conference on Craniofacial Morphogenesis and Tissue Regeneration and was elected to serve as 2015-2016 president of the Society for Craniofacial Genetics and Developmental Biology. In addition, he serves on the board of the American Association of Anatomists and the Society for Developmental Biology.

HOW MUCH CONTACT DO YOU HAVE WITH CHILDREN WITH TCS OR THE OTHER NEUROCRISTOPATHIES?

I have attended and spoken at the Treacher Collins Connection national conference, which is organized and sponsored by the parents of children with TCS. Meeting the parents of these children is inspiring and motivating. It reminds me that our work has an impact on their understanding of TCS.

Because TCS is a rare birth defect, it's unusual to see many children with the same condition in the same place. However, at the conference, I had the chance to see children with the syndrome having fun and running around, behaving like typical everyday kids.

Attending the meeting also was eye-opening because I learned about some of the non-medical problems that individuals with TCS and their families have to deal with. For example, parents often have difficulty in obtaining coverage for their children's surgery because the insurance companies frequently regard the operations as cosmetic.

WHAT DO YOU ENVISION AS THE ULTIMATE BENEFIT OF YOUR RESEARCH?

Our ultimate goal is to determine why specific birth defects occur in the first place and to identify the genes and the environmental factors or agents that cause them. If we can understand the origin and development of congenital disorders in enough depth, we may be able to come up with creative ways to prevent them from occurring.

WOULD PREVENTION INVOLVE A TARGETED GENETIC CHANGE?

No, in most cases that would be too difficult if not impossible, especially given the limitations of current technology. More likely it would involve a dietary or other type of intervention that protects the neural crest cells from being damaged during development. For example, today we know that folate can help protect brain and spinal cord cells during embryonic development. As a result, spina bifida and related open neural tube defects can often be prevented by mothers taking a specific amount of folic acid throughout pregnancy.

WORK LIFE BALANCE IS IMPORTANT TO YOU. WHY DO YOU ENCOURAGE YOUR TEAM MEMBERS TO TAKE BREAKS FROM THE LAB?

The research that we do in the lab is like a never-ending story. There are highs and lows, but every time we answer one question or hypothesis, we generate another ten. The number of experiments that we want and need to do, therefore, continues to increase exponentially. Just like reading a book, when you get to the end of a chapter, sometimes you need to put it down for a while and do something else. I believe that even individuals who are very passionate about their work need to recharge, to take a break and refresh. It's all about balance.

HOW DO YOU RECHARGE?

By cycling with my wife and our two children, both of whom were born in Kansas City, and playing water polo with a team in Kansas City. During the summer, I also participate in one or two triathlons.

DO YOU FIND THAT YOU GENERATE YOUR BEST IDEAS WHEN EXERCISING?

When I'm playing water polo, I usually am not thinking about science because I'm too busy thinking about how to beat my opponent or prevent myself from drowning! It's a remarkable way to relieve stress. Cycling and running, however, are often free-thinking times when I do think about science, but at the same time, I also simply enjoy the fresh air and the sights and sounds around me.

HOW OFTEN DO YOU RETURN TO YOUR HOMETOWN OF SYDNEY, AUSTRALIA?

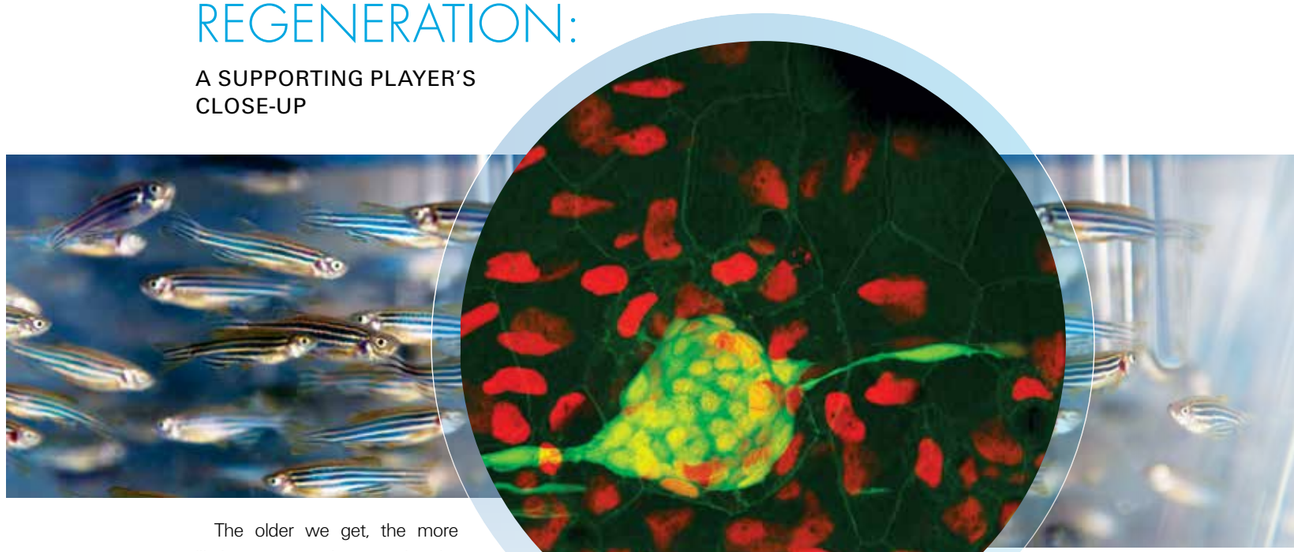
I visit my family in Sydney about every two to three years. It is particularly nice to go home during a Kansas City winter because then it is summertime in the southern hemisphere and I get to enjoy the surf beaches that I don't get in Kansas City. Sydney combines the best parts of San Francisco and San Diego. It's a great city to live in and visit.

WHAT DO YOU AND YOUR FAMILY ENJOY ABOUT LIVING IN KANSAS CITY?

Kansas City is a very comfortable, easy city to live in with a lively art, music, entertainment and food culture. Basically, anything we want to do, except perhaps go to the beach, is quite accessible. Also, Kansas City does not have the crowd or traffic issues of much larger cities. As a result, I have no idea what a traffic jam is like anymore. Not having to spend a lot of time being stuck in traffic means that I have more time with my family and more time to run, and cycle, and enjoy all that Kansas City has to offer.

ORCHESTRATING HAIR CELL REGENERATION:

A SUPPORTING PLAYER'S CLOSE-UP



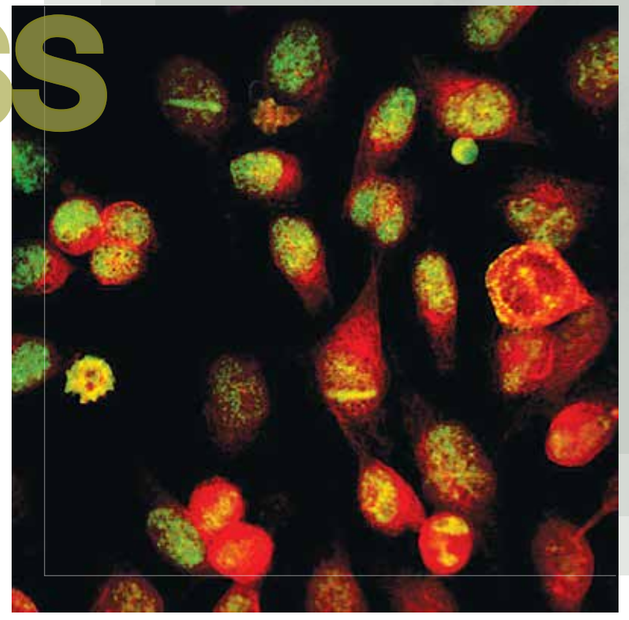
The older we get, the more likely we are to lose our hearing. This hearing loss is caused by death of or damage to our inner ear sensory hair cells, which, unlike their zebrafish counterparts, are irreplaceable. Researchers at the Stowers Institute, led by Associate Investigator Tatjana Piotrowski, PhD, studied the underlying mechanisms of this regeneration process in zebrafish sensory hair cells, in hopes to provide basic insights needed to develop therapies for hearing loss in humans.

Zebrafish use a lateral line organ system to discern water movement. The lateral line is composed of sensory organs called neuromasts that are made up of centrally-located sensory hair cells and surrounding support cells. "We've known for some time that fish hair cells regenerate from support cells," Piotrowski explains, "but it hasn't been clear if all support cells are capable of this feat, or if subpopulations exist, each with different fates."

By carefully tracking the location and behavior of each individual support cell following hair cell damage, first author of the study Andrés Romero-Carvajal, PhD, determined that the dividing support cells follow one of two trajectories: differentiation into hair cells or self-renewal to maintain a reserve. These lineage fate decisions are location-specific, as differentiation into hair cells occurs toward the center of neuromasts and self-renewal occurs at opposite poles of the structures, and depend on the interplay between Notch and Wnt signaling coming from the neuromast. The loss of hair cells in the center results in a transient suppression of Notch signaling, which triggers the differentiation of support cells into hair cells. "We found that Notch directly suppresses differentiation (of support cells into hair cells), and indirectly inhibits proliferation by down-regulating Wnt signaling," Piotrowski explains. Eventual restoration of neuromast hair cells restores this balance between Notch and Wnt signaling, ensuring that not all support cells answer the call to regenerate through proliferation and differentiation.

These findings were reported in the August 10, 2015, issue of *Developmental Cell*.

STRESS TRIGGERS KEY MOLECULE TO HALT TRANSCRIPTION OF CELL'S GENETIC CODE



FOR ALMOST THREE DECADES, INVESTIGATORS JOAN CONAWAY, PHD, AND RONALD CONAWAY, PHD, HAVE STUDIED THE FUNDAMENTAL MECHANISMS THAT DRIVE TRANSCRIPTION, THE FIRST STEP IN GENE EXPRESSION.

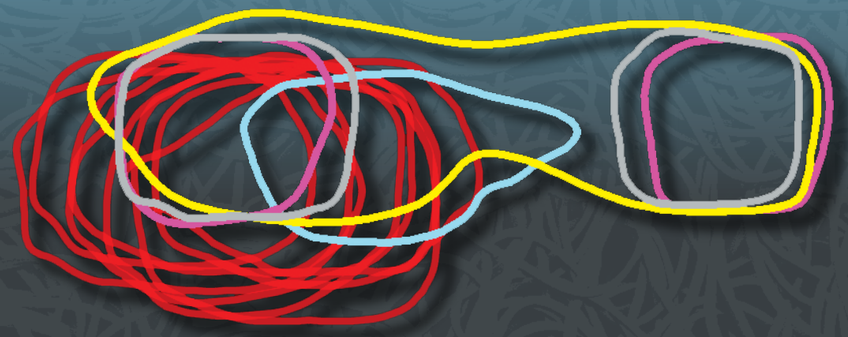
Many of their discoveries have focused on elongin A, a molecule that plays two roles in this process — acting as a facilitator by restarting transcription machinery when it sputters or a destroyer by marking the transcription machinery to be decommissioned when it is stalled.

In a study led by the Conaways, researchers at the Institute and at Kochi Medical School in Japan have now discovered how elongin A morphs between these two identities. It was previously known that as a facilitator, elongin A partners with its sister proteins elongin B and C, and as a destroyer, it also brings in another protein, Cul5, to form a complex known as ubiquitin ligase. Juston Weems, PhD, a postdoctoral researcher and first author of the study, decided to track and monitor this elongin A-Cul5 association in healthy and stress-induced cells. By fluorescently tagging the proteins, Weems and colleagues found that the complex not only rapidly accumulated in response to localized DNA damage that is known to stall polymerase, but also in response to various other stimuli that are not known to stall polymerase.

"It's possible that the ligase forms under these circumstances just in case the polymerase gets 'stuck' on some critical, newly activated genes," says Joan Conaway. "On the other hand, these results raise for the first time the possibility that elongin A might play a positive role in gene activation by some mysterious mechanism that we'd really like to understand." Understanding whether elongin A plays a previously unexplored role in gene activation will be the next step for these researchers.

This study was published in the June 12, 2015, issue of *The Journal of Biological Chemistry*.

INNOVATIVE IMAGING TECHNIQUE REVEALS NEW CELLULAR SECRETS



Key parts of mitosis rely on tiny, tube-shaped structures, called spindle pole bodies (SPBs). Until now, the nanoscale process of SPB duplication has remained elusive to researchers, largely due to the resolution limits of current optical microscopy. A common alternative, electron microscopes, can see much smaller objects, but do not work on living cells.

Now, a team of researchers from the Stowers Institute for Medical Research and the University of Colorado Boulder has devised a novel optical technique — a combination of structured illumination microscopy (SIM) and single-particle averaging (SPA) — to resolve individual components of SPB duplication in living yeast cells. SIM makes laser-based interference patterns that change based on what they interact with, doubling the resolution of optical microscopes, while SPA brings tiny objects and their locations into sharper focus by averaging many images into one "typical" picture. Using this method, the team was able to achieve a precision within a 10-30 nm range. Visualizing the SPB duplication using the SIM-SPA technique, the researchers were able to determine that these structures form at different times than previously thought. They also spotted a number of never-before-seen structures used in SPB duplication.

Associate Investigator Sue Jaspersen, PhD, who led the study, credits the collaboration between her lab and members of the Institute's scientific support groups for developing this technique. "I told them what I wanted to investigate and they made it happen," Jaspersen says. "At the cutting edge of resolution, every little part matters. Research Specialist Zulin Yu, PhD, of the Microscopy Facility made sure we took the best images and Research Advisor Jay Unruh, PhD, helped us analyze them in fantastic new ways." According to Jaspersen, the SPA-SIM technique is applicable to a wide variety of subjects beyond SPB structure and has opened up new possibilities in the field of cellular imaging.

These insights were published online September 15, 2015, by *eLife*.

By Lakshmi Chandrasekaran

FROM MOUNTAIN TRAILS TO PRAIRIES:

THE MAKING OF A RESEARCHER

Imagine growing up in a beautiful mountain valley in Nepal, nestled among the Himalayas. Long walks along the winding mountain trails would certainly increase anyone's appreciation of the living world. Stowers Summer Scholar Bishwas Sharma grew up in these surroundings, and his foray into biology has followed a path similar to the one up the mountains.

Bishwas is currently an undergraduate in his senior year at St. Olaf College, a liberal arts college in Minnesota. Influenced by the chemistry teachers in his high school, Bishwas planned to major in chemistry initially. But a philosophy of science class that he took in his sophomore year at St. Olaf became a life-altering event.

"My professor asked us to bring to class any random object from outside (at the time it was -40 degrees Fahrenheit in Minnesota) and I collected a random twig. We put our object in a sterile broth and observed it under the microscope. Within a week, I saw little bacteria and even protozoa swimming there. I could not believe they came from that little twig! I was mesmerized watching them grow under the microscope," he recalls.

Sharma's interest in biology was sufficiently stoked by the experiment.

After a few didactic biology courses, he was ready to try his hand at bench research. Unfortunately, being an international undergraduate student posed many limitations. "Many research programs that are government funded require citizenship or permanent residency of the students working on research projects," he comments.

Having heard about the Stowers Summer Scholars Program from previous participants, Sharma decided it would be a great opportunity to get the hands-on research experience he was looking for. "This program has proved to be a perfect fit for me. The Institute provides an intense research environment and also sponsors international students. My experience confirmed my fascination with biology," he adds.

Joining Stowers Investigator Alejandro Sánchez Alvarado's lab for the summer was an exciting adventure for Sharma. "I worked on a model organism called planaria. They are little self-regenerating flatworms. I had never even heard of them before I joined the program. It is really captivating to me how much this organism can contribute to studying and understanding regeneration." says Sharma.

Advancing biology requires the discovery of new tools and scientific methods. With planaria being a relatively new research model organism, the necessary tools to perform protein analysis are very limited. Sharma was assigned to a project that is attempting to bridge this gap.

An Zeng, PhD, a postdoctoral researcher in the Sánchez Alvarado Lab who was responsible for mentoring Sharma was impressed with his mentee. "Bishwas displayed significant enthusiasm and motivation for learning new things, and for applying them to our work and driving our research forward," Zeng says.

Outgoing and extroverted, Sharma enjoyed socializing with the other summer scholars away from the lab. As someone who loves exploring new cities, he found Kansas City's Westport district a haven for good food and entertainment. "Kansas City was a lot of fun and I will miss it," he says fondly.

Sharma values the connections he has made with researchers at the Stowers Institute. He confesses that this has been an eye-opening experience. Interacting with people from various backgrounds has helped him clarify his future career goals. "Previously, I worried that my liberal arts background would put me at a disadvantage. But talking with a few postdocs who have a liberal arts background has helped me realize the advantages of a broader view," he explains.

Exuding a newfound confidence from his research experience in the Stowers Summer Scholars Program, Sharma no longer doubts that graduate school is the right path for him.

"After coming to the Institute, graduate school doesn't seem so scary," he says with a laugh. "The interaction with predoctoral researchers about their research has helped me prepare for what will be expected of me when I pursue a doctoral degree at a research institution." After completing graduate school, Sharma envisions a career in teaching.

Sharma's research experience at the Institute inspired him and revealed something quite valuable. "Research often occurs more slowly than expected and it's not just about getting the results. Sometimes you run into negative results. The important thing I learned was how to find a better direction and keep moving forward."

SCIENTISTS IN THE MAKING

One way to nurture tomorrow's scientists is to cultivate their scientific curiosity through up-close and direct experiences with innovative research. The Stowers Summer Scholars Program strives to do just that by providing undergraduate students the opportunity to perform hands-on cutting-edge research.

Funded by the Stowers Foundation - an entity distinct from the Stowers Institute that encourages and funds unique educational programs - the Stowers Summer Scholars Program gives students the opportunity to interact with leading scientists and pursue independent research projects for a ten-week period at the Institute. The research projects span diverse fields of biology and provide exposure to topics at the frontiers of biology.

The program draws undergraduates from all across the United States and the world. In fact, the Stowers program is one of only a few in the US that admits international students, who augment the variety of backgrounds and experiences of this group of eager and inquisitive minds.

Although summer scholars spend a substantial amount of time in the lab, they also find the time for social activities such as movie nights and excursions to places in and around Kansas City such as baseball games and local botanical gardens.

At the conclusion of the program, summer scholars have an opportunity to communicate their research as part of a poster session at the Institute. They not only take away valuable scientific knowledge and first-hand research experiences, but also networks and friendships with Stowers researchers and other summer scholars. Often this experience proves to be an important first step toward a career in science.

Ingredients for scientific success: tenacity and curiosity

The Graduate School of the Stowers Institute for Medical Research has gathered eight scientifically curious and highly tenacious individuals from around the world for its 2015-2016 class of predoctoral researchers. These are important attributes for success in a rigorous program that stresses critical thinking and development of experimental expertise. Upon completing six months of modular course work and another six months of laboratory rotations, these novice researchers will be challenged to identify a significant biological question that they will investigate for the next several years of their lives.

Meet the eight unique individuals that comprise this class…

María Angélica Bravo Núñez

As a child growing up in Mexico, María Angélica Bravo Núñez gravitated to science as a way to better understand the world around her. She joined the team of a university immunology laboratory while still in high school, and has worked in a lab setting ever since.

Bravo Núñez earned a BS degree in genomic sciences at the National Autonomous University of Mexico. She explored genomic engineering at the Center for Genomic Sciences in Cuernavaca, Mexico, where she helped create a genetic biological computer using *Bacillus subtilis* as a model system. Her team won a top award in the 2012 iGem Latin American Jamboree for their entry.

Encouraged by a friend to visit the Stowers Institute, her campus visit and interview sealed the deal. Bravo Núñez is certain that the Stowers Institute will help her grow into a better scientist and a better person.

Viraj Doddihal

Viraj Doddihal credits his parents for starting him on the road to the Stowers Institute, a journey that began in a small, rural town in the southern Indian state of Karnataka.

They supported his interest in science by enrolling him in a competitive high school in the city of Mysore. Doddihal's rigorous high school education prepared him to attend a five-year BS and MS degree program at the Indian Institute of Science Education and Research.

Doddihal first learned of the Stowers Institute while investigating planarian regeneration at the Institute for Stem Cell and Regenerative Medicine. Eager for the opportunity to learn more from a pioneer in that field, he applied to the Stowers Institute's predoctoral research program.

Cassandra Eubanks

Cassandra Eubanks became interested in science as a teenager after her father was diagnosed with multiple sclerosis, an immune disorder that attacked his nervous system and ultimately claimed his life.

Eubanks has undergraduate degrees in mathematics and philosophy but chose to return to school after a stint teaching high school chemistry. She earned a BS degree in chemistry from the University of Missouri-Kansas City in 2014.

She sees the Stowers Institute as a place where her desire to unravel problems intersects with what humanity needs—new approaches for targeting disease—and hopes to help people in ways that science wasn't able to help her father.

Nicole Nuckolls

Nicole Nuckolls was set on becoming a speech pathologist until she took her first freshman biology class at Rockhurst University in Kansas City. Immediately hooked on biology—she admits to reading her textbook for fun—Nuckolls discovered an unparalleled sense of joy and excitement from being in the lab.

Nuckolls boosted her research experience at the Stowers Institute at the urging of her advisor. She worked in the laboratory of Scott Hawley, PhD, where she identified female meiotic mutants in *Drosophila melanogaster* and graduated with a BS degree in biology in May, 2015.

She is happy to continue her research where she feels at home. Nuckolls plans to use the knowledge she gains to investigate the world around her in a career devoted to science.

Kyle Patton

A concussion from a high school football game coupled with curiosity about evolution sparked Kyle Patton's fascination with neuroscience and evolutionary developmental biology.

Patton actively pursued both interests after high school at Wheaton College, designing his own major in interdisciplinary studies combining biology, psychology, and chemistry. His master's thesis explored the role of stress on the evolution of learning and memory, and drew extensively from the work of Stowers Associate Investigator Kausik Si, PhD.

Patton is thrilled to continue his research at the Stowers Institute and learn from some of the foremost leaders in neuroscience and evolutionary developmental biology.

Irina Pushel

Irina Pushel credits her parents, who moved her family from Belarus to the United States when she was 6 years old, for setting her on a scientific path.

She developed a passion for research as a high school student at the Illinois Mathematics and Science Academy, and chose to continue her education at Michigan State University because the institution allowed her to conduct research in her freshman year. While at Michigan State, Pushel earned a BS degree in biochemistry and molecular biology/biotechnology.

A strong believer in the importance of basic research, Pushel chose the Stowers Institute because of its community of individuals committed to the same goal.

Kevin Ramos

Becoming an independent researcher is a lifelong dream for Kevin Ramos, whose boundless curiosity and ambition emerged in childhood. Growing up in an environment with little emphasis on education challenged Ramos, but it also taught him the self-motivation and resourcefulness he needed to pursue a career in science.

Ramos drew on those skills to earn a BS degree in biology with a chemistry minor from Boston's Suffolk University in 2014.

A firm believer of learning through doing, Ramos sees himself as a good fit for the Institute, which seeks individuals who "stress critical thinking and rapid development of experimental prowess." He looks forward to a future spent pursuing cutting-edge research, exploring the unknown, and tackling complex questions.

Jelly Soffers

A native of the Netherlands, Jelly Soffers felt a special connection to the Stowers Institute during her interview visit, when she read the Institute's motto "Hope for Life" inscribed in Dutch ("Hoop Doet Leven") on the soaring glass panels above the library's fireplace.

Soffers earned a BS degree in molecular life sciences at Maastricht University in 2009. While there, she became intrigued by the pathways that regulate growth and development, and how mechanisms that regulate embryonic growth become dysregulated during cancer development. Soffers explored that relationship further while working toward a master's degree in oncology and developmental biology.

Soffers intends to maximize her time at the Institute, filling her "scientific backpack" with the skills and experiences necessary to prepare herself for a challenging postdoc position, with the hopes of one day starting her own research group.

Learn more about these amazing individuals at www.stowers.org/gradschool/predocs.

MD/PHD STUDENT MAGGIE PRUITT LANDS PRESTIGIOUS PREDOCTORAL FELLOWSHIP

Maggie Pruitt, an MD-PhD student at the University of Kansas School of Medicine, who is conducting her doctoral research in the laboratory of Stowers and HHMI Investigator Peter Baumann, PhD, was awarded a Ruth L. Kirschstein Predoctoral Individual National Research Service Award through the National Cancer Institute. This highly competitive award supports talented predoctoral students throughout PhD and MD phases of training.

Pruitt investigates the basic biology of telomeres and telomerase. Telomerase is a protein complex that elongates chromosome ends prior to cell division and is critical for cell survival. But in many cancers, telomerase is overactive which allows the cells to continue extending their telomeres and replicating.

More specifically, Pruitt studies the effects of telomere sequence on telomerase activity and telomere function. With this study, she hopes to identify strategies that will impair telomerase activity or destabilize telomeres in cancer cells, and ultimately improve therapy for some cancer patients.

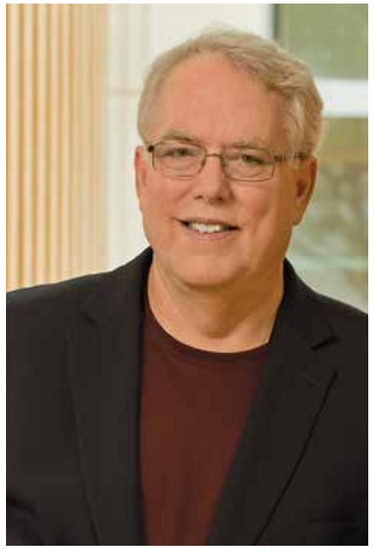
YU RECEIVES GRANT FUNDS TO STUDY SENSE OF SMELL

Associate Investigator Ron Yu, PhD, has received a five-year grant from the National Institute on Deafness and Other Communication Disorders, part of the National Institutes of Health, for his proposal to investigate the role of specialized, neuronal connectivity patterns in regulating the way sensory information is processed and perceived. Specifically, Yu plans to create an anatomical sensory mapping of odor perception.

Yu and his team plan to exploit their understanding of the development of the olfactory system to gain insights into the contribution of specific connections to odor coding and perception. By genetically altering sensory connections and perturbing the anatomical map, they will probe odor discrimination and recognition. Using advanced electrophysiology and optical imaging techniques they will illuminate the impact of the altered connections.

Because cognitive deficits in psychiatric disorders related to sensory processing and perception often arise from disruptions in neural sensory circuits, this research could reveal how brain function can deteriorate due to disruptions in normal neuronal connections.

DEDICATION AND RESEARCH EARN HAWLEY AMERICAN CANCER SOCIETY RECOGNITION



Thirty-two years of continuous research funding from the American Cancer Society, with eighteen grants totaling over $2.1 million, combined with ten years as an American Cancer Society Research Professor has earned R. Scott Hawley, PhD, investigator and dean of the Graduate School at the Stowers Institute for Medical Research, a research service award from the American Cancer Society. Hawley received the award from the High Plains Division of the American Cancer Society at the Kansas City Cattle Baron's Ball on June 13, 2015.

"Scott Hawley has changed the way the community thinks about cancer research," says Bridgett Myers, senior director of Community Engagement of the American Cancer Society in Kansas City. "Dr. Hawley has a gift for explaining and discussing cancer research in a way that our volunteers and donors can relate to and understand. He gives us hope that what we are doing to raise the money, to support the research, is truly making a difference in the fight against cancer. We are forever grateful to Dr. Hawley for his service to the American Cancer Society."

"I love reaching out to people to tell them why research matters and why it needs their support," says Hawley. "I want cancer to one day become a disease that can be treated in the pharmacy. There are a few tools like that already out there, and there are a few more coming, but there is still a long way to go. In times like these when funding from other sources is very tight — in many cases levels of support for cancer research aren't being maintained, much less increased — it is going to be up to us to stand up and gather the resources we need to make these big advances possible."

AMERICAN ACADEMY ELECTS MODEL ORGANISM PIONEER SÁNCHEZ ALVARADO

Stowers Institute and Howard Hughes Medical Institute Investigator Alejandro Sánchez Alvarado, PhD, is known for his groundbreaking work on the biology of the planaria—a flatworm model organism known for its regenerative abilities. He was among the first to demonstrate that RNA-mediated genetic interference (RNAi), a biological process in which RNA molecules inhibit gene expression, could work in organisms other than nematodes. His work paved the way for the first successful screen to identify planarian genes involved in tissue regeneration. His research has provided important insight into biological processes crucial for regeneration and essential for the normal development of animals and humans.

This year Sánchez Alvarado was inducted as a fellow into the American Academy of Arts and Sciences. He shares the honor of membership in this esteemed society of scholarship, civil dialogue and useful knowledge with some of the world's most accomplished leaders from academia, business, public affairs, the humanities and the arts.

Since its founding in 1780, the American Academy has elected leading "thinkers and doers" from each generation. The current membership includes more than 250 Nobel laureates and more than 60 Pulitzer Prize winners.

"We are proud of this prestigious national recognition for Dr. Sánchez Alvarado," says David Chao, PhD, president and CEO of the Institute. "The well-deserved honor recognizes the kind of pioneering work that the Institute seeks to foster and inspire."

Sánchez Alvarado considers it a privilege that his work is being recognized and has no plans to rest on his laurels. "I am grateful that the Institute allows me to ponder complex ideas and pursue them experimentally. Moving forward, I intend to continue to ask questions and plumb the depths of life in a way deserving of this honor," he affirms.

ASSOCIATE INVESTIGATOR MATT GIBSON RECEIVES NIGMS GRANT

Associate Investigator Matt Gibson, PhD, has received a grant from the National Institute of General Medical Sciences, a division within the National Institutes of Health. The competitive grant will fund a project designed to expand the fundamental knowledge of an unexplored area of basic biology.

During development of multicellular animals, layer upon layer of epithelial cells provide the architectural structure for nearly all organ shapes and functions. However, not much is known about cell division within this epithelial architecture.

In humans, a majority of metastatic cancers originate from epithelial cells that divide excessively and escape their normal confines. This process is called epithelial-to-mesenchymal transition (EMT). Gibson's proposal includes using genetic, biochemical and proteomic analysis of fruit flies to study the molecular mechanisms that coordinate cell division in healthy epithelia and how defects in these mechanisms can result in EMT.

ALEX'S LEMONADE STAND FOUNDATION AWARDS IMAGING DIRECTOR KULESA INNOVATION GRANT FOR PEDIATRIC CANCER RELATED WORK

Neuroblastoma is a devastating solid tumor cancer that arises in the nervous system outside the brain and spinal cord and is often fatal in children. The tumors are derived from embryonic neural crest cells that fail to properly migrate or mature. It is known that a variety of molecular signals guide these processes in the embryo, but it is unclear how defects in these signals contribute to the disease. Stowers Institute Director of Imaging Paul Kulesa, PhD, has received an Innovation Grant from Alex's Lemonade Stand Foundation to pursue this very question.

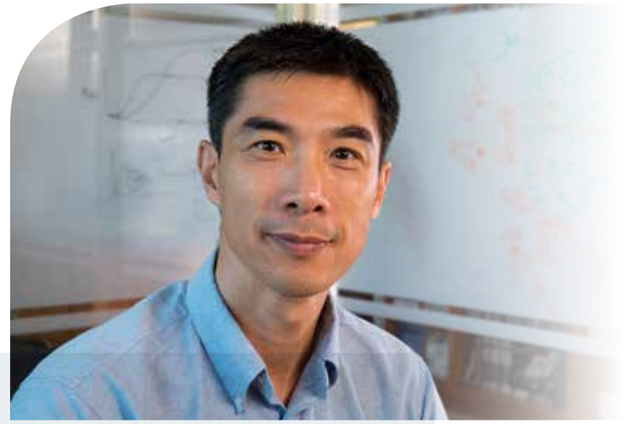
"We plan to leverage our expertise in neural crest biology and state-of-the-art in vivo imaging to address this roadblock," explains Kulesa. He and his research team recently discovered a critical role for TrkB, a receptor for brain-derived neurotrophic factor, during sympathetic nervous system development. High expression of TrkB has been correlated with poor prognosis for neuroblastoma patients. The Kulesa laboratory plans to develop an embryonic quail transplantation model that will allow the lab to study the effect of mis-regulation of TrkB on normal development and human neuroblastoma cell behaviors. By studying changes in TrkB expression and other signaling pathways they hope to be able to develop and evaluate targeted personalized therapies.

Innovation Grants, which were among the first grants given by Alex's Lemonade Stand Foundation, were created to provide critical and significant seed funding for experienced researchers with novel and promising approaches to finding the causes and cures for childhood cancers. Kulesa will receive $250,000 over two years.

SAB RECOMMENDS PROMOTION AND RENEWAL

Every spring a small number of highly distinguished scientists meet at the Institute to review the work of Stowers investigators. This group, called the Scientific Advisory Board, weighs the merits of laboratory heads and their research programs to ensure the high-caliber, innovative research that has become synonymous with the Stowers Institute name. This year, the board recommended renewal of two researchers.

Ron Yu promoted to Investigator



Ron Yu, PhD, focuses his lab's research on olfaction. Olfaction, or sense of smell, is a critical means of perceiving and translating information from the environment. In animals it helps them detect food, predators and mates, but sense of smell can also be a conduit for strong emotional connections that influence behavior.

Yu's lab investigates the neural mechanisms involved in the recognition of odors and their chemical receptors. By dissecting the neural circuitry that processes chemical signals called pheromones, Yu hopes to discover which neurons are responsible for which behaviors and exactly how that information is processed. Understanding these signals and the brain circuits they activate may shed light on how the brain translates senses into meaningful behaviors.

In related work, Yu is developing a new imaging tool that will visualize multiple signals within the neuronal circuit architecture at a much greater resolution. Yu and his team plan to use the new tool to image an entire mouse brain and its neuro-circuits. *(See related article on page 8).*

Jerry Workman renewed as Investigator

Jerry Workman, PhD, in pioneering work, was one of the first scientists to discover that histones are not just architecture of DNA, but also play a vital role in transcribing DNA into RNA. Workman and his team described how certain groups of proteins send signals that initiate the unwinding of tightly bound histone balls so that DNA is readable and available for genes to be turned on or off.

More recently, Workman's focus has been on histone modifications that generate signals that regulate information contained in the DNA sequence. Complexes of proteins are responsible for histone modification and one such complex that Workman's group discovered is the SAGA complex. This complex plays an important role in the initiation of gene expression in which DNA is transcribed to RNA.

The team has discovered new functions of these complexes that could play a role in cancer therapies and found subunits within the complexes that control cell migration.

WELCOME THE NEW NEIGHBORS

ASSISTANT INVESTIGATOR
RANDAL HALFMANN, PHD

What remains of the child raised on a cattle farm in central Texas are the good manners and an intrinsic curiosity for the natural world around him. From participating in his high school's Future Farmers of America (FFA) organization to completing graduate studies at the Massachusetts Institute of Technology (MIT), Randal Halfmann, PhD, has immersed himself in the scientific aspects of his experiences. Supported by a FFA scholarship, Halfmann attended Texas A&M and majored in genetics. Encouraged by his mentor at A&M, he applied for a National Science Foundation fellowship and pursued graduate work at MIT.

It was at MIT where he first began to think seriously about studying particles of misfolded proteins, called prions. At the time, prions had a notorious reputation for being the cause of mad cow disease and its human counterpart, Creutzfeldt-Jakob disease. But Halfmann's research over the next five years produced two notable papers that helped identify at least one positive attribute of these problem proteins.

In a 2009 *Cell* paper and a 2012 *Nature* paper, Halfmann and colleagues demonstrated that in some yeast, prionization — a cascading assembly of proteins into aggregates that alter the normal flow of biological information — actually helped yeast adapt to environmental change. This ignited Halfmann's interest in identifying the adaptive behaviors aggregated proteins might foster.

With this novel idea and support from competitive grants, Halfmann landed a position at The University of Texas Southwestern Medical Center, bypassing traditional postdoctoral training. There, he began a research program that looked at how proteins aggregate together into prion form and how that change is passed from parent yeast to daughter yeast. Additionally, he showed that some prions function as part of immune response in mammalian cells.

Attracted by the generous support provided to investigators, Halfmann joined the Stowers Institute in August and will continue his research of proteins. Halfmann is excited by the promising future he sees at the Institute. "The Institute puts science first and removes obstacles that might keep scientists at other places from doing what they do best," he says.

ASSISTANT INVESTIGATOR
NICOLAS ROHNER, PHD

While a student at the Max Planck Institute in Germany with Nobel Laureate Christiane Nüsslein-Volhard, Nicolas Rohner, PhD, had no idea that his research on fish genetics would intersect with the medieval history of the region where he grew up.

Scale-less carp is a dietary mainstay of the Franconia area of Germany where Rohner spent his youth. Turns out the findings in a 2009 *Current Biology* paper authored by Rohner pinpoint the genetic mutation that monks selected for when domesticating the carp in the Middle Ages. Rohner showed that a gene called Fibroblast Growth Factor Receptor 1 is necessary for fish to develop scales, and mutations in this gene lead to the desired phenotype.

Although Rohner's current line of research investigates why vertebrates, and fish in particular, exhibit diverse genetic traits, his initial foray into science led him down a different path. Rohner earned a bachelor's degree at Friedrich-Alexander University in Erlangen, Germany, and went on to research antibodies that target leukemia cells while obtaining an MS degree in biology.

By then, Rohner was looking for new challenges and decided to pursue a doctoral degree in developmental biology using zebrafish as a model organism. This research avenue eventually led him to the fish he currently focuses on — the sightless cavefish, *Astyanax mexicanus*.

Cavefish have adapted to their dark environment and thus, now lack eyes. In addition, the fish may feed only once a year when food is available. Rohner was intrigued by their ability to maintain good health under such adverse conditions. His research, published this year in the *Proceedings of the National Academy of Sciences*, found that cavefish have a mutation in a gene for a receptor called MC4R, apparently allowing the fish to binge eat to the point of obesity. In normal fish, intact MC4R serves as a satiety signal and even the human counterpart of MC4R is mutated in some forms of inherited obesity.

In his lab at the Stowers Institute, Rohner will continue his studies focused on the genetic basis of adaptation and metabolism. He is energized by the freedom he now has to take risks in research. "I came in with what sounded like a very unusual model system to study obesity," he explains. "The Institute has provided me the tools to develop it into an important one to help us better understand developmental biology and eventually provide new insights into human health."

BACKSTAGE PASS

"Neither snow nor rain nor heat nor gloom..." Much like the United States Postal Service motto, the grounds-keeping crew at the Stowers Institute maintains a park-like campus year-round in all weather conditions. They pamper and prune, and mulch and mow to keep the grounds in a stunning state so that members of the Institute and visitors alike can enjoy the beautiful surroundings.

The grounds and gardens include multiple fountains and waterfalls, a babbling brook, meandering pathways, a shaded gazebo, and acres of perfectly manicured lawn.

GROUNDSKEEPING BY THE NUMBERS

80,000
gallons of water in fountains

15,000
pounds of ice melt spread on sidewalks and driveways throughout winter

5,200
number of flower bulbs planted every fall to bloom in the spring

3,000
average number of annual flowers planted each spring

2,200
sprinkler heads used to water the lawn and landscape

1,500
individual shrubs in beds that require trimming

230
trees on the campus

100
yards of mulch spread around trees and landscape beds each year