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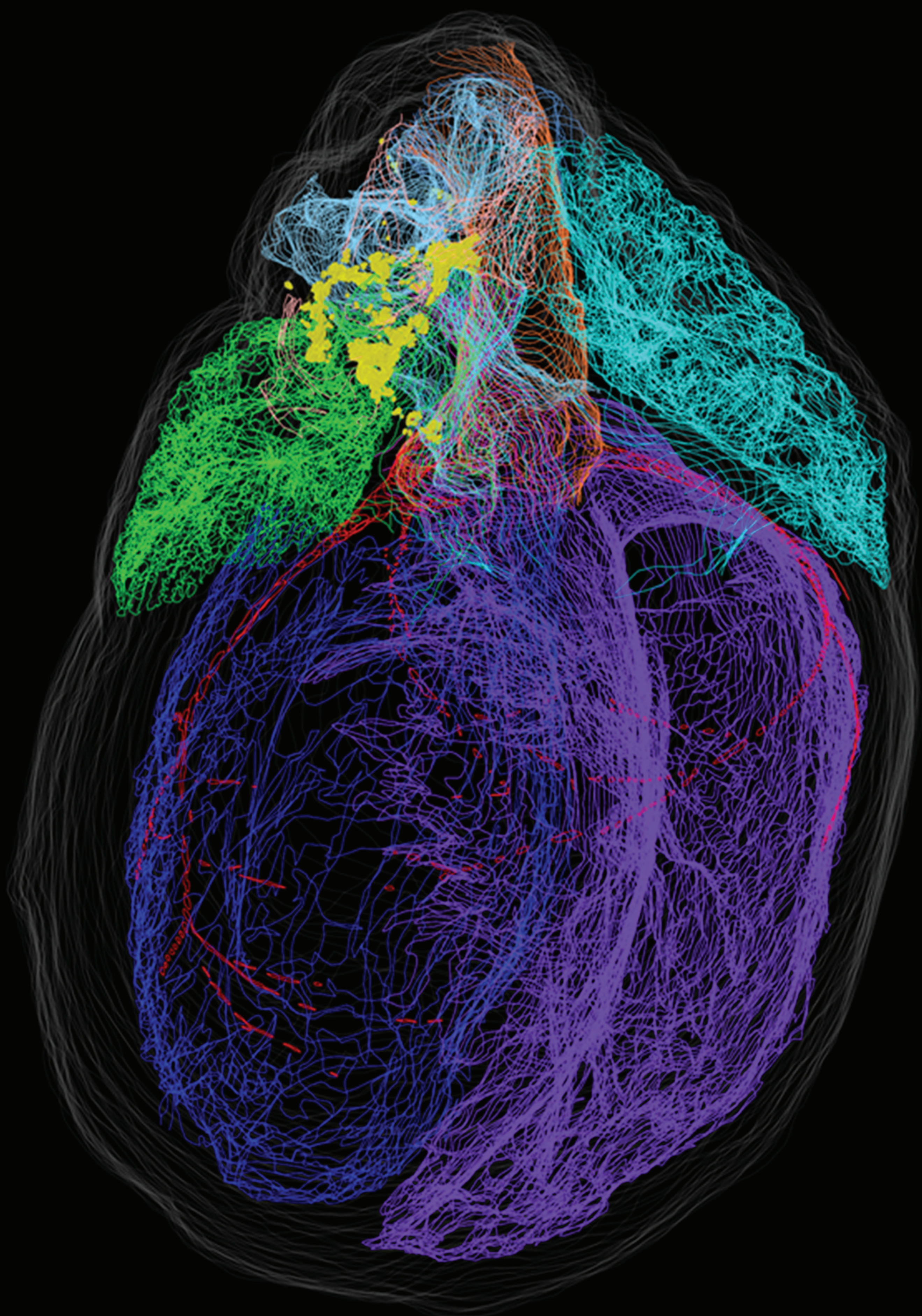


The Heart's "Little Brain"

Researchers develop the first ever 3D map of the heart's nervous system, providing a foundation for understanding the complexities of heart health.

BY **KARUNA MEDA**

On the computer screen, a 3D model of a heart rotates seemingly in mid-air, a carousel of colors and contours. Amidst the blue and purple waves that denote the heart's powerful muscles sit a cluster of yellow dots. To anyone else, it looks like a meaningless blob. But to James Schwaber, PhD, and Raj Vadigepalli, PhD, it represents a culmination of nearly three decades of work, a long-awaited key to a world of unanswered questions.

Let's rewind...

> **"The map demonstrates that the local control of the heart is much more nuanced than we've been able to appreciate..."**
> *Dr. Vadigepalli*

Thirty years ago, the scientific and medical communities were desperately trying to find answers for heart disease, which has been the single biggest killer in the United States since 1921. Attention turned to a massive and meandering network of nerves called the vagus nerve — it carries signals from the brain, the master organ of our body, to other organs, including the heart. Scientists found that when these signals weren't sent properly, it could actually impair heart health and even lead to heart failure. When they poked the vagus nerve with an electrode to help jump start it, they found that an ailing heart could actually pump better! It was a thrilling finding. But there was a problem: the scientists didn't know where the vagus nerves ended in the heart — was it a certain chamber, or a muscle, or an electrical node? Which of these connections could explain how the vagus nerve affects heart health?

Around the same time, the early 1990's, researchers found that the heart had nerve cells or neurons that were akin to the ones that made up the brain. In other words, the heart had its very own nervous system that could function independently of the brain! Affectionately called "the little brain" of the heart, it became a point of fascination in the field — why does the heart need its own nervous system anyway? How does it help the heart function? It also became a potential target for the vagus nerve. Could a connection between the brain and the "little brain" be the key to restoring heart health?

Drs. Schwaber and Vadigepalli have been at the forefront of trying to answer these questions for the last 25 years, giving critical insight into the heart's nervous system. In the last five years, serendipity brought them together with like-minded experts and advanced technology that allowed a major breakthrough: the first-ever 3D map of the heart's "little brain." It is a map that gives an unprecedented look at not only how the neurons are organized in the heart — that undiscerning blob of yellow dots — but also their biological properties. For the first time, our researchers are able to appreciate the spatial *and* functional relevance of the heart's neurons in keeping the organ healthy, giving us new clues about how to tackle the longstanding issue of heart disease.

Tracing the Connections between the Heart and the Brain

The connection between the heart and the brain goes back to 1884, when the psychologist William James famously described this scenario: "Imagine you are walking through the woods, and you come across a grizzly bear. Your heart begins to race. You feel afraid, and you run." The concept suggests that the physical reaction (a racing heart) drives the emotional experience (fear). This interplay has always fascinated Dr. Schwaber.

In the early 1990's, he was at the DuPont Company in Wilmington, Delaware, and was particularly interested in the burning question at the time — how does the vagus nerve connect to the heart?

By then, researchers discovered that the vagus nerve connected to the sinoatrial node, which controls heart rate. "That connection made sense for heart health," says Dr. Schwaber. "But I wanted to know if the vagus nerve connects to the ventricles, the chambers that pump blood to the rest of the body. A connection here could be beneficial too."

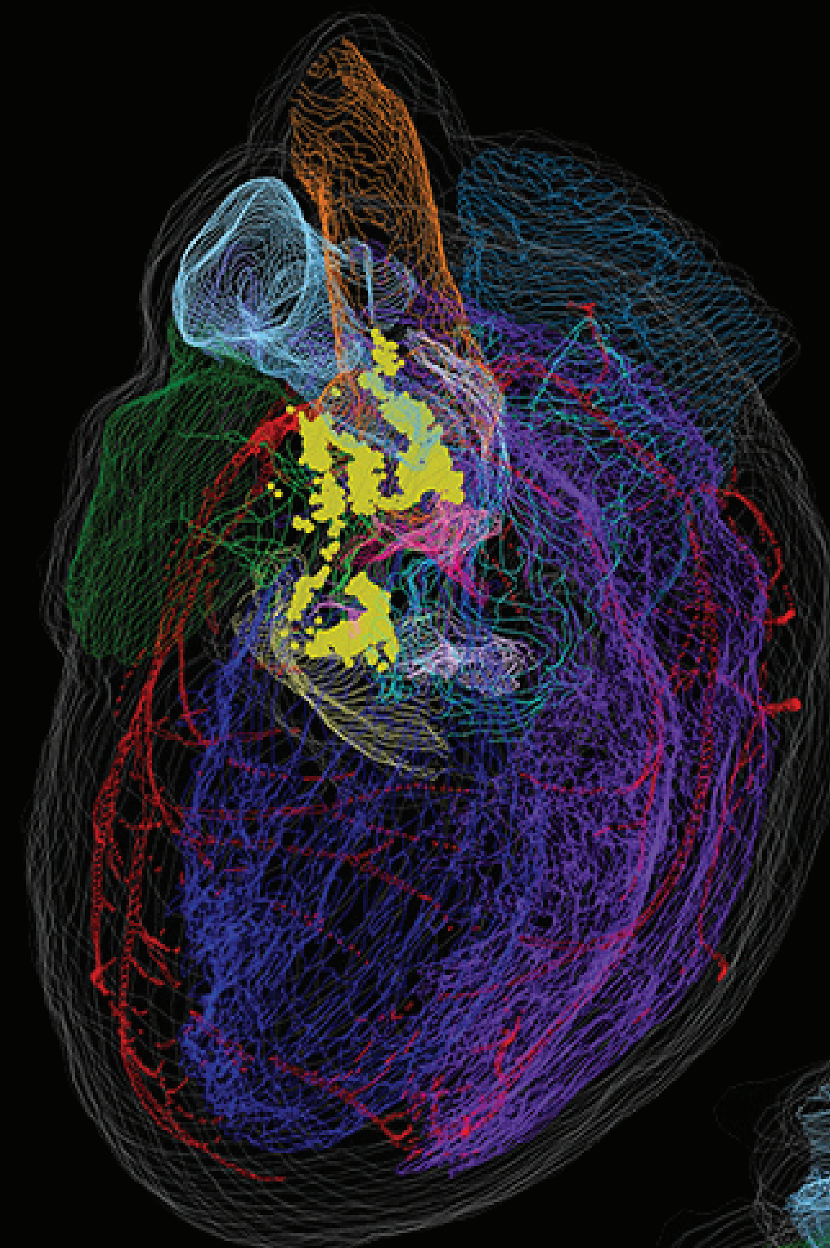
To shed light on this, Dr. Schwaber turned to a molecular biologist at DuPont by the name of Lynn Enquist, PhD, who was developing a novel technique using a modified virus to label multiple relay points in a neural pathway. When Drs. Schwaber and Enquist injected the virus into the ventricles of the rat heart, they traced the connections all the way back to the neurons in the brain that gave rise to the vagus nerve. They had just shown that the vagus nerve does indeed connect directly to the ventricles!

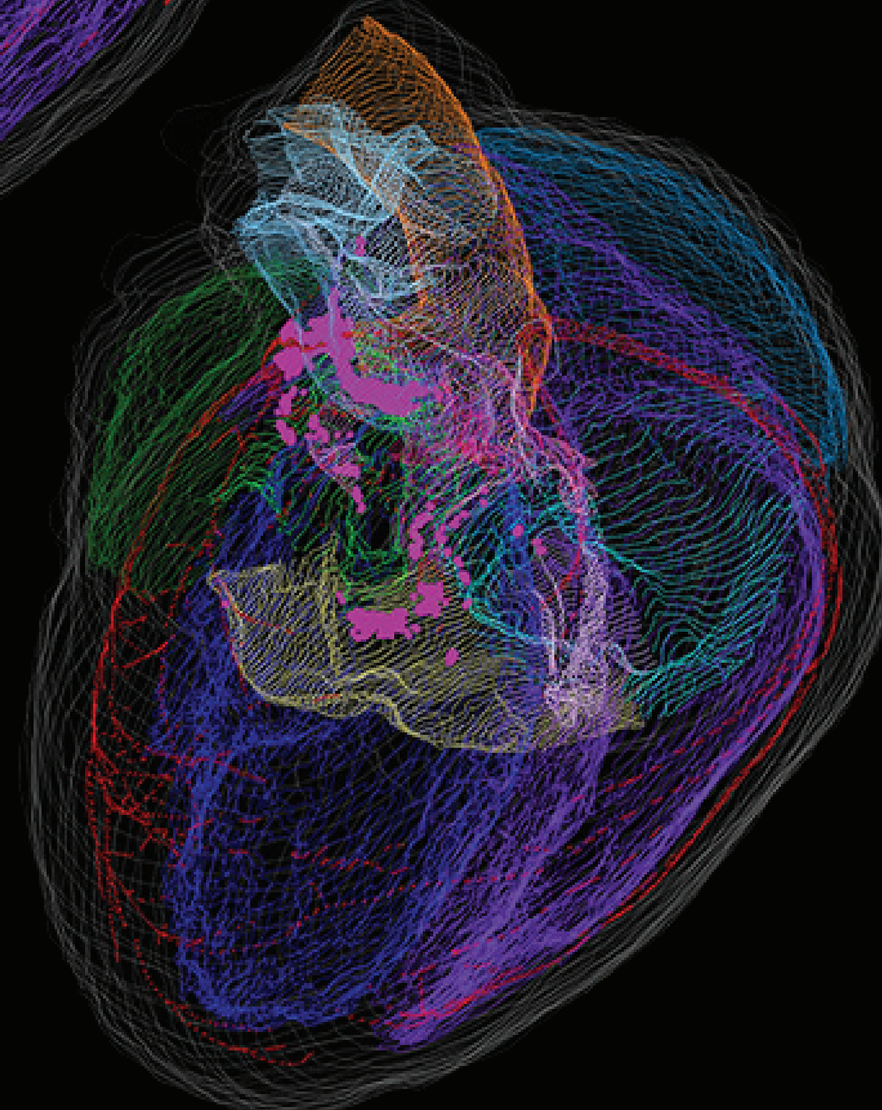
It was a major finding that challenged the accepted view on how the vagus nerve might affect the heart. But there was push-back — some believed that the observation was simply an artifact of the new tracing technique. The field needed convincing with more conventional methods.

Dr. Schwaber had help from a former lab member — Frank Doyle, PhD — who had just started his first faculty position in chemical engineering at Purdue University and recruited a postdoctoral researcher, Zixi Cheng, PhD. They were able to validate the earlier findings, but their tracing revealed something else — as nerve fibers left the heart to go the brain, some looped back into the heart. In fact, they were going back to the heart's "little brain," which had just been described in 1991 by a scientist named Dr. J. Andrew Armour. It was still poorly understood, and the researchers were unsure what to make of this internal loop. This is where Dr. Vadigepalli entered the scene.

The Heart's "Little Brain" through the Eyes of an Engineer

Dr. Vadigepalli was pursuing his PhD in systems engineering at Purdue University in Dr. Doyle's lab when he was pitched this idea of a new circuit between the brain and the heart.





Male vs. Female: *A comparison of the "little brain" in the male heart (yellow dots) and female heart (pink dots). The distribution of the neurons is different, and there are fewer neurons in the female heart.*

*Images captured by **Shaina Robbins, MS***

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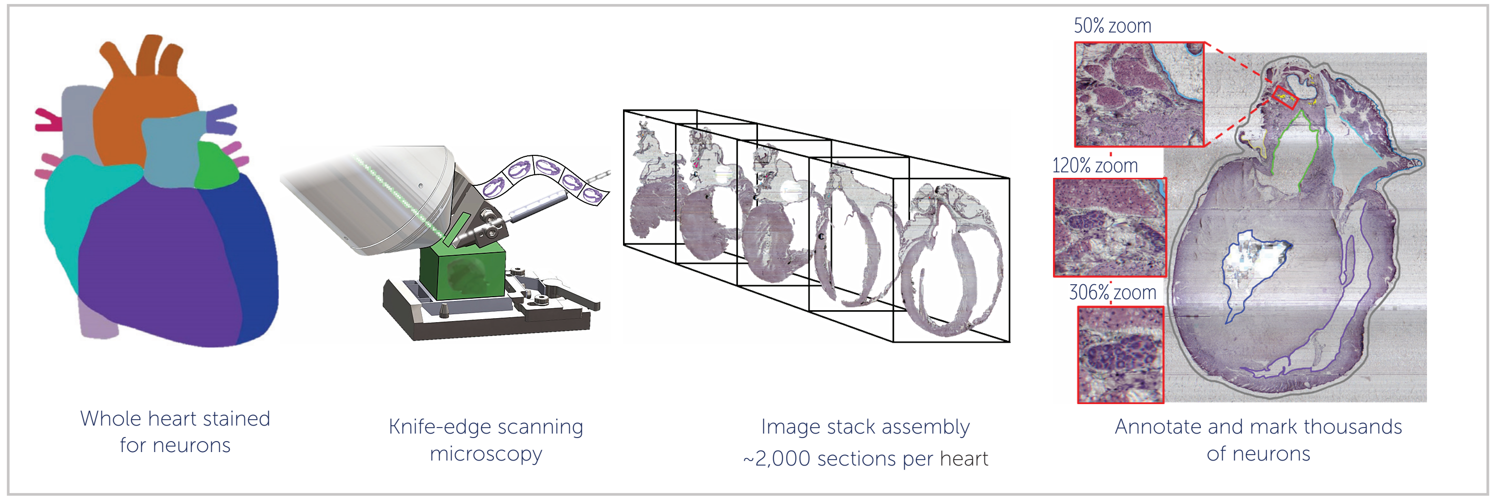

How to build a 3D heart: *The fully digitized, single-cell resolution images were painstakingly made by slicing a heart stained for neurons, and then mapping those labeled-image sections onto a computational scaffold.*

"...the heart's 'little brain' resembled an internal loop that engineers call local controllers — so what is this one adding to the control of the heart?"

Dr. Vadigepalli

"The last time I took a biology class was in high school," says Dr. Vadigepalli. "I didn't know anything about all the controversy that surrounded this new anatomy – but it was fascinating to me from an engineering perspective."

The heart reminded Dr. Vadigepalli of a control system, a bread-and-butter concept of engineering. Control systems are all around us – think about the cruise control in your car that maintains a safe speed, or the thermostat that works to keep your home at a preferred temperature. These systems work in such a way that when you change the information input, they can adjust to achieve the desired outcome.

"The heart receives input from the brain about our internal state and environment, and it adjusts to maintains outputs like heart rate, blood pressure, etc. accordingly," explains Dr. Vadigepalli. "But the nerve fibers that were found going back into the heart's 'little brain' resembled an internal loop that engineers call local controllers – so what is this one adding to the control of the heart?"

This became the basis of Dr. Vadigepalli's thesis work, from the mid to late 1990's. Through mathematical modeling, he found that when the internal loop was on, it could fine tune how the heart responds to signals from the brain. This improved the heart's performance and made outputs like heart rate more reliable. When it was off, the heart's "little brain" couldn't correct local disturbances, and the external loop to the brain had to be recruited instead, making the control system less efficient. Without the internal loop playing this role of damage control, the heart could become erratic, leading to an irregular heartbeat or arrhythmia – or so the modeling predicted.

This work finally shed some light on the function of the heart's "little brain" and provided evidence for it to be an ideal target for the vagus nerve. It also gave rise to new opportunities for integrating systems engineering into the field. But these mathematical models were hypothetical, and needed to be proven with experimental work. Many questions remained.

A SPARC of Serendipity

In 2000, Dr. Schwaber and Dr. Vadigepalli brought their respective expertise to Jefferson, joining forces in the new Daniel Baugh Institute for functional genomics and computational biology, which Dr. Schwaber led.

For the next decade, they switched focus from the heart to the brain, studying the "central controller." Scientists had developed maps of the brain in different animal models that could pinpoint the position of individual neurons and the genes they expressed. These maps gave insight into how neurons could be spatially organized in intricate circuits, and how their genetic identity determines their function in these circuits. It was exactly the kind of map they needed for the heart, says Dr. Vadigepalli, to help them understand the function of the "little brain." But such a map did not exist yet.

In 2015, their luck began to change when a NIH funding program called 'Stimulating Peripheral Activity to Relieve Conditions' or SPARC was conceived. It brought together researchers who studied different organ systems and their communication with the brain, a concept called interoception. The interplay regulates vital bodily functions like digestion and breathing, but can also influence our mood and cognition. Much of the field of interoception has focused on the vagus nerve, which in addition to heart health, can affect the health of the liver, the gut, the lungs, etc. The ultimate goal of SPARC is to develop therapeutic devices that can change electrical activity in nerves, like the vagus, to treat conditions like heart failure, inflammatory disorders, diabetes, and more.

"SPARC filled this massive void in the field and reignited our interest in the 'little brain'," says Dr. Schwaber. "But there was so much more we needed to understand about its anatomy and function."

As they revisited their old stomping grounds in the heart, serendipity struck again. They came across two new technologies — one, an automated imaging technique that could precisely reconstruct any tissue in 3D; the second, a software that could build manipulable images and videos of these 3D reconstructions. Both companies were shopping for customers. It was a match made in scientific heaven.

Drs. Schwaber and Vadigepalli recruited a core team of trainees between their two labs — Sirisha Achanta, lab manager at the Institute, Alison Moss, a graduate student, Jonathan Gorky, a MD/PhD student, Shaina Robbins, a research assistant — and went about building a methodological protocol from scratch. They brought their old colleague, Dr. Cheng, now at the University of Central Florida, back into the fold as well, along with his graduate student Clara Leung.

By 2019 the team had created a dual approach pipeline — one using the imaging technologies to build a precise 3D reconstruction of the entire rat heart viewable via computer screen; and the other using a technique called laser capture microdissection to sample single neurons for gene expression analysis. This allowed them, for the first time ever, to build a 3D map of the heart's "little brain" in the rat — one that showed the individual positions of the neurons within the heart's anatomy, as well as their genetic properties.

"We've created a foundation for developing 3D maps for other organs in animal models and ultimately in humans, in health and disease. **The possibilities are endless.**"

Dr. Schwaber

A Map to Endless Possibilities

As the researchers behold the floating 3D heart on the computer screen, each turn illuminates new questions about the cluster of yellow dots that represent the "little brain" — how are the neurons organized around key structures of the heart? Can this influence how hard and fast the heart pumps? How do the neurons communicate with each other, and with signals from the brain? Does this organization and communication change in heart disease? Given that heart physiology differs between males and females, does the "little brain" differ between sexes?

The 3D map has revealed some of these answers, amidst hitherto unknown complexity of the heart's "little brain." The researchers found that the neurons in the rat heart are clustered around the sinoatrial node, positioning them optimally to monitor and regulate heartbeat. The map also allowed them to pinpoint how the "little brain" is organized and wired differently in male vs. female rats; for instance, although they found fewer neurons in the female heart compared to males, it doesn't impact the heart's essential functions. This provides clues as to why there may be differences in cardiovascular disease between men and women.

The team also explored the "little brain" in the pig heart, which is more anatomically comparable to the human heart. They found that unlike neurons of the brain, which are often defined by the chemical they release — either ones that augment or depress activity, etc. — neurons of the heart had much more fluid expression of these chemicals. It was as if the heart's neurons contained multiple identities. The various permutations and combinations allow the neurons in the "little brain" to fine tune how the heart responds to signals from the brain. This validates Dr. Vadigepalli's thesis work, which demonstrated this fine-tuning in mathematical models.

"The map demonstrates that the local control of the heart is much more nuanced than we've been able to appreciate," says Dr. Vadigepalli. "It suggests that a single drug that turns heartbeats up or down, may not be as effective as one that hits the right combination of targets. There is much more to explore in developing new therapies for heart disease."

The researchers are currently using the map to understand how the vagus nerve connects to the neurons of the "little brain" and provide highly anticipated evidence for how the vagus affects heart health. They hope their findings, and work from their SPARC colleagues, will also provide the physiological underpinnings for how mental states (e.g. stress), and interventions that alter them (e.g. meditation), affect the whole body.

"We've created a foundation for developing 3D maps for other organs in animal models and, ultimately, in humans, in health and disease," says Dr. Schwaber. "These maps are the key to the brain-body connection. The possibilities are endless."