The American Heart Association’s mission is to be a relentless force for a world of longer, healthier lives. The foundation of that work is funding lifesaving research. The organization is proud to be the leading not-for-profit funder of heart disease and stroke research in the U.S. Its research program, which dates back more than seven decades, has funded more than $4.6 billion to target heart disease and stroke, two of the world’s leading causes of death.

One way the AHA prioritizes research is by funding Strategically Focused Research Networks (SFRN) to accelerate progress in specific areas of need. In 2015, the AHA began its second SFRN, focused on hypertension, a major risk factor for heart disease and stroke. This $15 million SFRN invested more than $3.7 million to the following four institutions:

- Cincinnati Children’s Hospital to study target organ damage in youth
- Medical College of Wisconsin to examine genetic changes in patients with hypertension
- University of Alabama at Birmingham to look at blood pressure patterns impacting organ disease; and
- University of Iowa to study ways to predict hypertension during pregnancy

One of the most notable features of this SFRN was the requirement that each center’s work include a basic, clinical and population science component. Several center directors said this model was a way to create translational teams that conducted research more efficiently and effectively.

“Our SFRN included about 15 or 20 investigators,” said Paul Muntner, Ph.D., M.H.S., FAHA, FASH, Center Director from the University of Alabama at Birmingham. “Having so many people working together, there was clearly synergy, where the sum was truly greater than the parts.”

Mark Santillan, M.D., Ph.D., FACOG, FAHA, a principal investigator from the University of Iowa, agreed. “The SFRN model has been really smart for the AHA to take on because it addresses all aspects of a particular disease,” he said. “It was natural for us because we were always working between the bench and the bedside.”

Beyond the collaboration within each institution, researchers were also required to collaborate across centers throughout the multi-year project. Each site worked with one another on everything from publications to intellectual exchanges. Creating meaningful, replicable ways to collaborate across institutions was one of the project goals, said Oversight Advisory Committee Chairperson Daniel Lackland, Dr.P.H., FAHA.

He outlined a three-pronged benefit to the SFRN’s work: (1) at the project level; (2) at the center level; and (3) at the network level — how each center’s work related to the issues of hypertension.

“[This SFRN] really challenged these researchers to work together and create a synergistic, high-impact model,” Lackland said. “They put together something very unique.”
If there was one word to describe the relationship between researchers at the four Hypertension SFRN centers, it would be “synergy.” Each center reported working together across disciplines and institutional borders to achieve network goals.

Cincinnati Children’s Hospital
Center Director: Elaine Urbina, M.D., M.S., FAHA
At Cincinnati Children’s Hospital, researchers worked in new ways — across institutions and across the country — collaborating on target organ damage in youth with primary hypertension. The SFRN model was an ideal opportunity to advance the science of high blood pressure research in youth, said Center Director Elaine Urbina, M.D., M.S., FAHA. She is also a leader in the International Pediatric Hypertension Association, which had long been interested in such an opportunity.

“The AHA’s SFRN funding opportunity really gave us the tools we needed to take that next step,” she said.

Given the smaller percentage of youth with hypertension (compared to adults), the research required a multi-site approach that was not achievable through traditional funding mechanisms.

“This is the type of study in pediatrics that cannot be done in a single center,” Urbina said.

The project’s population researchers studied the effect of salt intake on DNA methylation in salt-sensitive rats. They found that salt intake changes DNA methylation in T-cells, in humans? They answered this by studying DNA methylation in a group of 50 people, after giving them a low-salt diet for two weeks. They found significant changes in DNA methylation in T-cells. Second, “can DNA methylation in T-cells explain differences in blood pressure or other characteristics between identical twins?” Researchers studied close to 150 pairs of monozygotic twins, seeking to “take genetics out of the equation” by creating a situation where genetics were nearly identical, Liang said. They found T-cell DNA methylation may explain part of the effect of several lifestyle factors.

The population project used a cohort of approximately 3,000 African Americans first established about 25 years ago. At that time, the original researchers collected samples from study participants. For this project, the team went back to the cohort and analyzed current health. They identified a surprising strong association between DNA methylation and blood pressure and a remarkable improvement in predicting if participants would go on to develop cardiovascular health concerns when the researchers included DNA methylation as a predictor.

Current models can predict 10-year risk of cardiovascular disease at about 70%, Liang said. “With the methylation marks that we found in this AHA program, we could improve that to about 80%. It may seem like a small increment, but that’s actually a pretty big increment in terms of clinical application.”

“DNA methylation features are really adding substantial value to the current model,” he said.

It’s his hope that this SFRN’s work will lead to DNA methylation applied at the health care professional level, making it easier for patients to understand their risk for cardiovascular disease.

Medical College of Wisconsin
Center Director: Mingyu Liang, M.B., Ph.D.
At the Medical College of Wisconsin, researchers hypothesized that dietary salt intake, maternal dietary exposures and other lifestyle factors cause genome-wide changes in DNA methylation (one of the mechanisms of epigenetics — which may influence the expression of genes) and that these changes contribute to hypertension or can serve as markers of hypertension and cardiovascular diseases.

Researchers analyzed DNA methylation at near genome-wide scale. The clinical, population and basic science teams worked together with a remarkable synergy to study epigenetic changes in humans and animals to help identify new ways of controlling high blood pressure, said Center Director Mingyu Liang, M.B., Ph.D.

Although the university’s team had discussed working in such a collaborative way previously, the SFRN’s creation solidified the arrangement.

“The three projects in our center really functioned as a single project,” Liang said. “That really was very, very helpful for us to be able to drive the science forward in a way that is relevant to humans and also deep in science.”

The basic science team studied the effect of salt intake on DNA methylation in salt-sensitive rats. They found that salt intake changes DNA methylation in T-cells and the kidney substantially and that these changes contribute to the development of hypertension in salt-sensitive rats.

Clinical researchers sought to answer two questions. First, “How will low sodium intake change DNA methylation in T-cells, in humans?” They answered this by studying DNA methylation in a group of 50 people, after giving them a low-salt diet for two weeks. They found significant changes in DNA methylation in T-cells. Second, “can DNA methylation in T-cells explain differences in blood pressure or other characteristics between identical
University of Alabama at Birmingham (UAB)
Center Director: Paul Muntner, Ph.D., M.H.S., FAHA, FASH
University of Alabama at Birmingham researchers focused on what blood pressure looks like during sleep to better understand hypertension’s 24-hour effect on cardiovascular and renal health.
“It’s important that people have their blood pressure measured outside of the doctor’s office,” said Center Director Paul Muntner, Ph.D., M.H.S., FAHA, FASH. “For many people, the blood pressure they experience outside of their doctor’s office, when they go about their everyday activities, has a stronger association with cardiovascular disease risk.” That is the key take-away from our research.

The basic science team used animal models to study the mechanisms through which salt could affect 24-hour blood pressure patterns — and also to study whether genes control blood pressure. Clinical researchers studied the role of early mechanisms of preeclampsia, we have the opportunity to develop novel modalities to more robustly prevent preeclampsia before it starts or gets worse.

Population scientists studied the predictive capabilities of copeptin as a biomarker for preeclampsia. The team has published that it is predictive of the development of preeclampsia as early as six weeks of gestation. The team’s discovery has led to multiple patents with the hope of bringing this predictive test to the clinic. The university’s work on these topics continues in multiple avenues, funded by grants from several different sources, including the National Institutes of Health.

Center Director: Curt Sigmund, PhD, FAHA
At the University of Iowa, researchers focused on predicting hypertension in pregnancy. They sought a reliable early marker of preeclampsia to help diagnose this often difficult-to-pinpoint condition. The center’s work was led by director Curt Sigmund, Ph.D., FAHA.

“Preeclampsia is really hard to diagnose,” said Mark Santillan, M.D., Ph.D., FACOG, FAHA, one of the center’s principal investigators. “We have a marker for preeclampsia that is elevated as early as the sixth week of gestation, and stays high throughout pregnancy.”

“Our work, which has now been corroborated by other labs, has demonstrated that early pregnancy vasopressin dysregulation is not just predictive of the development of preeclampsia; but it is also a cause of the disease,” he said. “By identifying the early mechanisms of preeclampsia, we have the opportunity to develop novel modalities to more robustly prevent preeclampsia before it starts or gets worse.”

The center’s basic research focused on vasopressin-induced preeclampsia in a mouse model. (Vasopressin, a hormone released by the pituitary gland, is important in blood pressure regulation.) Multiple team publications demonstrate that early vasopressin elevation in the model replicates many crucial facets of human preeclampsia. With a model that replicates human preeclampsia well, researchers are investigating multiple therapeutic options to potentially translate to human therapy.

Clinical researchers studied the role of early vascular dysfunction and elevated copeptin in human preeclampsia. Copeptin is a marker for cardiovascular disease. The team has published that early human vascular dysfunction and early neurologic control of blood pressure are associated with the development of preeclampsia. These data further open the possibility of new preventive and therapeutic agents for preeclampsia.
The Fellows: A Closer Look

The Fellowship Program

With its Hypertension Strategically Focused Research Network, the American Heart Association offered a fellowship program that trained 13 postdoctoral scholars to be part of the next generation of multidisciplinary investigators.

The program was unique in two ways: It trained fellows to lead interdisciplinary research and provided them opportunities for cross-center collaborations. While fellows were assigned to one of the three specific teams at each SFRN center, they also regularly worked collaboratively, preparing them for careers in translational environments.

“This network forced them to be able to talk about how their research related to the population, the clinical and the basic science,” said Dr. Daniel Lackland, chairperson of the SFRN Oversight Advisory Committee.

Fellows had the chance to learn the “jargon” specific to each area of research, said Dr. Paul Muntner, University of Alabama at Birmingham Center Director. “It’s really a special opportunity for people to recognize and value and truly understand what other types of scientists do.”

These collaborations went beyond token requirements, Lackland said. In addition to regular meetings within center teams, fellows attended AHA Hypertension Council meetings, SFRN annual meetings, AHA research leadership academies and other national conferences. They worked alongside mentors and forged relationships with researchers at other institutions.

The fellows also got unique hands-on training.

Justin Grobe, Ph.D., FAHA, principal investigator of the University of Iowa’s basic science team, described his team’s work as, “in the trenches, together” – another layer to this collaborative approach that included almost everyone on the team working in the lab together.

“This format has proven exceptionally helpful, as it means that everyone is highly invested in project momentum and success, aware of technical obstacles, and working to overcome those challenges in real-time, and trainees are shoulder-to-shoulder with trainers,” he said.

Many of the fellows — nearly 70% — have remained in academia and research. They have all published scientific articles based on their research. In addition, many have won awards as a result of their research, and several have gone on to earn additional American Heart Association funding.

The result was overwhelmingly positive from the fellows, many of whom, such as Justin Thomas, Ph.D., from the University of Alabama at Birmingham, spoke highly of their team science experience.

“I think the SFRN has brought together scientists who might not normally work together to collaborate and address some critical issues in health,” he said. “In our case, we made a substantial impact in understanding hypertension and disparities in hypertension across age groups and different populations, and I believe this impact will allow us to better treat hypertension at a global level.”

Here are six of the fellows’ stories:

Gilad Hamandi, M.D.
Cincinnati Children’s Hospital
SFRN Hypertension Fellow, 2016–2018

Gilad Hamandi, M.D., was completing a three-year fellowship in pediatric nephrology at Cincinnati Children’s Hospital when he heard about the Hypertension SFRN Fellowship program.

“It was a perfect fit,” Hamandi said. “I was already interested in hypertension and this was an opportunity to learn more.” He spent 2016 to 2018 on the center’s clinical research team, studying 24-hour ambulatory blood pressure monitoring.

“I got to learn about hypertension, not only from the nephrology perspective, but also from the cardiology perspective,” he said. “I got to see a viewpoint of people from other centers and from other expertise regarding hypertension.”

That’s a viewpoint Hamandi also saw while learning from others at fellow-exclusive training opportunities and at joint meetings of SFRN centers. Meetings gave fellows a chance to consider, “how to think about your project, how to think about your future and how to develop your research career,” he said.

“Once you’re in these two years, you’re not doing any on-call time,” Hamandi said. “You are a little bit of a physician and a little more of a researcher.”

That time allowed him the opportunity to publish several papers and the experience to pursue his career goals upon returning to his native Israel. Hamandi is now a pediatric nephrologist at Schneider Children’s Medical Center, the only comprehensive, tertiary care hospital of its kind in the Middle East. It also has the biggest pediatric nephrology department in Israel. Hamandi’s goal is to develop a pediatric hypertension center there following the model at Cincinnati Children’s. For Hamandi, this SFRN fellowship gives him a one-of-a-kind background, he said. He has also earned a Hypertension Early Career Oral Award from the AHA Council on Hypertension.

“Pediatric hypertension is a unique area,” Hamandi said. “I really got a lot of extra knowledge in this area that gives me the ability to add more to this field specifically in Israel.”
John Henry Dasinger, Ph.D.
Medical College of Wisconsin
SFRN Hypertension Fellow, 2016–2018

For John Henry Dasinger, Ph.D., participating in the Hypertension SFRN Fellowship program offered an opportunity for collaboration he had not yet experienced in his career. Dasinger was in graduate school at the University of Mississippi when he heard about the program. He joined the basic science team at the Medical College of Wisconsin's Hypertension Center and was a fellow from 2016 to 2018.

“I really enjoyed working as a team to investigate the role of DNA methylation in hypertension on all levels of science,” he said. “Even though I was a fellow focusing on the basic science project, I was able to learn a great deal from all our project leaders, an experience I would not have had without the SFRN.”

Dasinger’s team demonstrated that dietary habits, such as the source of dietary protein that one consumes, can impact blood pressure through regulation of the immune system. Because the SFRN is designed as a synergistic model, he had collaborative opportunities such as observing the clinical science team as they collected tissues, or taking part in discussions of data collection and analysis for both clinical and population studies. When his SFRN fellowship ended, Dasinger moved to the Medical College of Georgia at Augusta University to continue his postdoctoral training, along with David Mattson, Ph.D., FAHA, the principal investigator of the center’s basic science project (who is now the Department of Physiology chair at Augusta University). He was also awarded an American Heart Association fellowship grant for this work.

“My time as a fellow in the SFRN has allowed me to build upon my SFRN project in new avenues of investigations such as how dietary habits impact the risk of developing metabolic syndrome in our rat model,” he said. “My time as a SFRN Hypertension fellow was extremely rewarding.”

Justin Thomas, Ph.D.
University of Alabama at Birmingham
SFRN Hypertension Fellow, 2015–2017

Justin Thomas, Ph.D., calls his involvement with the Hypertension SFRN Fellowship program “serendipity.” Thomas was looking for a career that allowed time for research. He interviewed with two of the center’s principal investigators and was drawn to how integrated their projects were. “It was not a difficult decision to jump on this opportunity,” he said, noting that the integration only grew with his involvement.

“My experience was amazing. The unique aspect of the AHA SFRN is that it takes a completely translational approach to research,” Thomas said. “As an SFRN fellow, I received training in all three areas of research. I think this translational research training opportunity is extremely unique and is something that benefits me today.”

Although he was assigned to coordinate the clinical project, where he examined the impact of dietary sodium intake on sleep apnea severity and sleeping blood pressure, Thomas also gained experience in basic and population science. In fact, nearly all of his published manuscripts were developed in coordination with the population science team, he said.

“The experience was transformative,” Thomas said. “I absolutely loved the collaboration with UAB scientists, as well as scientists at other institutions.” He formed collaborations with researchers from other institutions while a fellow, which have resulted in lasting relationships. For example, today he is co-investigator on a sleep ancillary study to the Coronary Artery Risk Development in Young Adults (CARDIA) study, which developed from a collaboration during his fellowship.

After completing his postdoctoral fellowship, Thomas earned a Career Development Award from the American Heart Association to study central and peripheral circadian markers among African Americans with dipping versus non-dipping blood pressure. That study is “uniquely translational,” developed thanks to the unique training and collaborative opportunities he had, Thomas said.

Today, Thomas has joined the team he’s spent years learning from. He is a tenure-track assistant professor in the Department of Psychiatry at the University of Alabama at Birmingham, and director of the Behavioral Sleep Medicine Clinic there.

“My mentors are now my colleagues,” Thomas said. “I can confidently say the SFRN Fellowship was instrumental in launching my career as an independently funded clinician scientist.”
Guorui Deng, Ph.D.
University of Iowa
SFRN Hypertension Fellow 2017–2019

Guorui Deng, Ph.D., was fresh out of graduate school at Wake Forest University when he became a Hypertension SFRN fellow at the University of Iowa in 2017. Deng said his mind quickly jumped into action when he heard about the project, thinking about the complexities of the research. Deng’s role focused on multiple basic science projects, which took a bioinformatic approach to identifying and reanalyzing relevant, publicly available RNA sequencing datasets to generate novel hypotheses on how dysregulated vasopressin signaling could promote preeclampsia development.

The best part of his work as a SFRN fellow, he said, was the chance to share findings with colleagues, both at the university, during weekly lab meetings with SFRN collaborators and at the national level during SFRN annual meetings.

"The collaborative nature of the SFRN is quite astonishing," Deng said. Weekly lab meetings allowed for ample discussion and for the team to improve experimental design based on feedback from experts in other disciplines. He also worked with previous SFRN fellows, creating unique collaborations such as one with a now-practicing OB-GYN specialist and Deng as a cellular/molecular biologist.

While a fellow, Deng has been noted for his productivity in publishing, both in manuscripts and in conference abstracts. He received multiple travel awards and also earned an additional postdoctoral fellowship from the American Heart Association, allowing him to study the role of central angiotensin II (a hormone that helps maintain blood pressure and fluid balance) signaling in the development of obesity.

"I had a great and collaborative experience as a SFRN Hypertension fellow," Deng said. "I was able to meet new mentors and greatly expand my laboratory skill set as well as improve my critical thinking, all of which are instrumental in helping me to establish myself as an independent investigator."

Brenda Mendizabal, M.D., M.S.
Cincinnati Children’s Hospital
SFRN Hypertension Fellow, 2015-2017

Brenda Mendizabal, M.D, M.S., has more than 15 years of medical studies and training under her belt. It was the years she spent in the American Heart Association Hypertension SFRN Fellowship program that uniquely prepared her to take the next step to where she is today, Mendizabal said. "I honestly don’t think I would have been able to start the program that I started here in Pittsburgh without it," she said. Today, Mendizabal is assistant professor of pediatrics and leads the pediatric preventive cardiology program at the Children’s Hospital of Pittsburgh. She learned critical skills needed for those roles while at Cincinnati Children’s Hospital, working with Hypertension SFRN Center Director Elaine Urbina on the center’s clinical research team.

The SFRN was a great opportunity because it offered the chance to see a project come to fruition “literally from the ground up,” Mendizabal said. “In any other kind of fellowship, it’s hard to really do that and continue with your clinical work.”

She has been able to build a program in Pittsburgh that models some of the key aspects she learned as a fellow. “Building leadership, seeing how collaboration is absolutely necessary in starting a preventive program, all of that I learned with SFRN,” Mendizabal said.

For example, as a fellow she was able to work closely with the team from the University of Iowa, meeting with them several times per year. “It’s very unique. I don’t think in any other opportunity would I have had that,” Mendizabal said.

In Pittsburgh, she has had the chance to build a comprehensive preventive cardiology program, working off an existing lipid program. Using what she learned as an SFRN fellow – both from the Cincinnati site and from other centers – she has put together “a pretty unique program,” Mendizabal said. The first thing she asked for in her new role was ambulatory blood pressure monitors – a tool she learned the importance of through her work with the SFRN.

“I’m trying to do some multi-disciplinary work,” she said, “but also have a full-blown program where we’re really encompassing lipid and hypertension, which had not existed.”
Louise Evans, Ph.D., stepped into the role of a SFRN hypertension fellow at the Medical College of Wisconsin as an accomplished, senior postdoctoral fellow who had already been focusing on hypertension research at MCW – in the same lab. Already familiar with the lab’s work and its team, she was an ideal fit for the role, center leaders said.

Working with the SFRN team was a unique opportunity for her as well, Evans said. While her time was focused on basic research, studying renal inflammation in salt-sensitive rats, the fellowship gave Evans the chance to collaborate with colleagues in new ways.

“The SFRN fellowship gave me the opportunity to work with a variety of investigators on a project that linked clinical, epidemiological and basic science. The opportunity to work with this diverse group of scientists on a broad, multidisciplinary project was the main advantage of the SFRN fellowship for me,” Evans said. “The opportunity to see our basic science project align so closely with a clinical project was particularly rewarding. It was also very helpful to gain a close insight into the clinical research process.”

Evans’ time as an SFRN fellow came at a critical point in her career. Immediately after her fellowship, she received a Scientist Development Grant from the American Heart Association, which led to her promotion to assistant professor at MCW. In 2018 she moved to the University of Minnesota as a research assistant professor, and today is in the process of setting up her own lab in the Department of Surgery at that school. She continues to study hypertension, focusing on the causes and consequences of renal inflammation in salt-sensitive hypertension.

Researchers in the Hypertension SFRN embraced collaboration at all levels — from the fellows to principal investigators to center directors. From co-authoring papers together to finding ways to assist in one another’s research, they created a model of cross-center partnership Dr. Daniel Lackland said is replicable.

“You have to look beyond what you normally might do. That took extra effort. It goes beyond a telephone call,” Lackland said. “We were able to show how it can be done.”

One example is the collaborative work of Cincinnati Children’s Hospital. Studying pediatric hypertension is by nature a multi-site endeavor, said Center Director Dr. Elaine Urbina, since pediatric hypertension is not common.

“The success of the CCH center was rooted in its ability to develop multiple collaborating centers,” she said.

Their SFRN was itself a collaborative effort, working with researchers at several institutions to complete the project, from nearby University of Cincinnati to Seattle Children's Hospital. Cincinnati Children’s shared their collaborative spirit by working with the University of Iowa Hypertension SFRN to gather data on preeclampsia from subjects enrolled in its SHIP AHOY (Study of High Blood Pressure in Pediatrics: Adult Hypertension Onset in Youth) study. Urbina’s team also gathered data in conjunction with the Medical College of Wisconsin for their Hypertension SFRN study.

The Medical College of Wisconsin team also collaborated with the University of Alabama at Birmingham to publish data on clinical and ambulatory blood pressure among African Americans in the Jackson Heart Study, the largest study of its kind studying African Americans and cardiovascular disease.

The University of Iowa also had notable collaborations with partners in industry and at other SFRNs, such as ongoing work with the Go Red for Women SFRN at Magee Women’s Research Institute and Foundation, to evaluate the role of vasopressin in post-partum hypertension.

“We’re getting this really wide view of what preeclampsia does to women,” said Dr. Mark Santillan, clinical project principal investigator at Iowa. “If I had to draw you our collaboration map it would be very branched out. We are continually doing work with others. The SFRN has been a great seed to keep it going.”

Collaborations

R

esearchers in the Hypertension SFRN
CONCLUSION

The goals of the Hypertension SFRN were clear when this work began in 2015:

- Produce a cadre of new investigators who will energize the hypertension field
- Produce new research
- Provide insights into and report on challenges and successful mechanisms for collaboration
- Identify programs/policies that result in individual lifestyle modifications that reduce risk and improve control of hypertension

The network achieved its goals, Lackland said. “If you look at the center studies, they have all been very strong,” he said. “They have made a great contribution.”

Collaboration between centers was a cost-effective way to maximize scientific impact, Lackland said. While it may have taken researchers’ time, it was well spent, he said.

“I think it showed that these groups can work together and the importance of them working together,” he said.

Creating four specific sites focused on hypertension also identified the centers as research hubs in this area, for future investigators interested in this topic, he said. That’s a helpful tool for the American Heart Association’s additional SFRNs, as well, Lackland said.

Ongoing SFRNs include networks focused on Heart Failure, Obesity, Children, Vascular Disease, Atrial Fibrillation, Arrhythmias & Sudden Cardiac Death, Cardiometabolic Health & Type 2 Diabetes Mellitus, and Health Technologies & Innovation.

Three additional networks have completed work, including: Prevention, Disparities and Go Red For Women. These sorts of collaborations are the future, said Dr. Muntner from the University of Alabama at Birmingham.

“Maybe 50 years ago or 100 years ago you would have a scientist in their lab by themselves making discovery. But science is much more complex now, that bringing together experts in different disciplines, across universities clearly results in better, higher impact results,” he said. “This model, if we want to have high-impact scientific discovery, provides a path for doing so.”
STRATEGICALLY FOCUSED RESEARCH NETWORKS