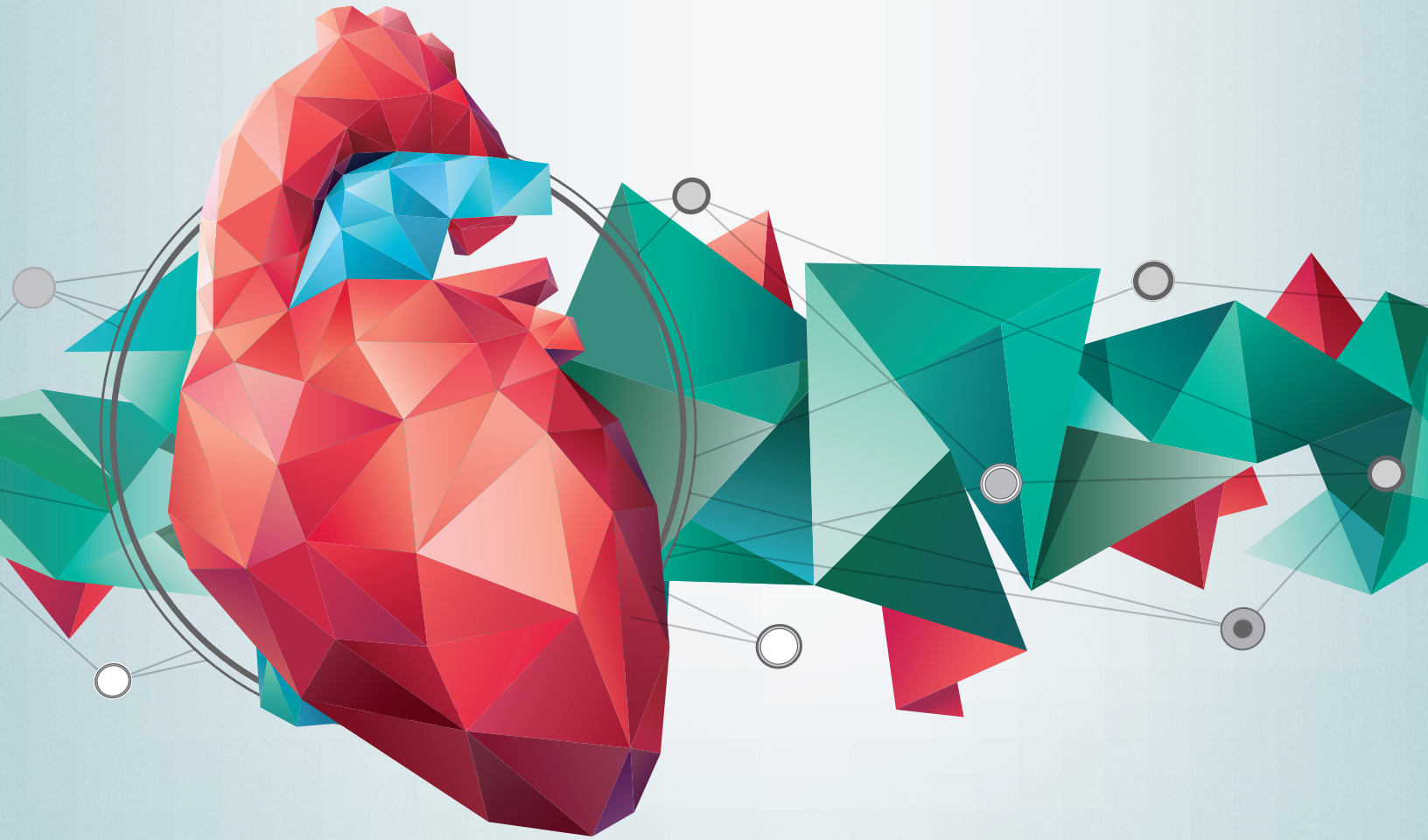
American Heart Association.

END OF NETWORK REPORT

CARDIOMETABOLIC HEALTH & TYPE 2 DIABETES



STRATEGICALLY FOCUSED RESEARCH NETWORK

For more than 100 years, the American Heart Association has been dedicated to fighting the No. 1 killer worldwide: cardiovascular disease. Research is a core part of its mission. Since 1949, the Heart Association has invested more than $6.1 billion in scientific innovation to help people live longer, healthier lives.

As science has evolved, the organization's research has kept pace. In 2014, the Heart Association established the first Strategically Focused Research Network (SFRN), a unique venture that brings together scientists from multiple institutions to study a common topic from different perspectives.

SFRN-funded scientists collaborate across disciplines to generate new approaches, ideas, and knowledge. The American Heart Association Board of Directors selects the topic for each SFRN, including the latest network: Cardiometabolic Health with a focus on Type 2 Diabetes Mellitus.

Cardiometabolic disease is a cluster of interrelated conditions affecting the heart, blood vessels, and metabolism. Fueled in part by high obesity rates, it affects as many as 3 out of 4 U.S. adults.

Dr. Loren Wold
Oversight Advisory Committee Chairperson

For this SFRN, the American Heart Association decided to study cardiometabolic disease with a focus on Type 2 Diabetes, which occurs when the body can't use insulin effectively and blood sugar rises, leading to serious health complications. About 36 million U.S. adults live with Type 2 diabetes, and many more have prediabetes, a major risk factor for developing the disease. Diabetes doubles the risk of heart attack, stroke and other heart complications.

To address these conditions, the Heart Association committed $14.8 million to establish the Cardiometabolic Health with a focus on Type 2 Diabetes Mellitus SFRN, giving researchers a critical opportunity to explore complex questions about these issues and develop better ways to prevent and treat them. Each SFRN center was asked to include a basic science, clinical science and population science research component. This SFRN also marked the first time the four Centers developed a unique, network-wide collaborative project.

The AHA awarded $3,445,000 to each of the four centers beginning in January 2020 and $1 million to support the network-wide collaborative project.

The four centers, along with their respective focus areas, were:

Brigham & Women's Hospital, to uncover why certain people with diabetes develop atherosclerosis and other cardiovascular complications.

Johns Hopkins University, to study cardiovascular risk factors in obesity, including diabetes, and their relationship to cell-signaling proteins.

New York University, to investigate defects in artery repair and their relationship to diabetes.

University of Iowa, to examine how secretions from the liver and fat tissue contribute to cardiovascular damage.

"We've known for years that patients with diabetes develop heart disease more frequently than those without it. With this unique SFRN, the Heart Association tackled the question of why that is, exactly," said Oversight Advisory Committee Chairperson **Loren Wold, Ph.D., FAHA**.

Although COVID-19 presented obstacles early on in the network, all four centers delivered "exceptional studies," Wold said, thanks in part to cross-disciplinary collaborations within and across the centers.

"This SFRN really brought together the dream team of world experts in cardiometabolic health and diabetes, all working together to come up with a new understanding of the problem," he said.

"It can't be overstated how important the Heart Association is when it comes to research like this, especially in these times of uncertain funding."

Cardiometabolic Health & Type 2 Diabetes SFRN Awardees & Oversight Advisory Committee

SFRN CENTERS: CARDIOMETABOLIC HEALTH & TYPE 2 DIABETES

Brigham and Women's Hospital

Center Director: Mark Feinberg, M.D., FAHA

From microscopic RNA signals to data from more than 100,000 patients, scientists at Brigham and Women's Hospital pieced together a new picture of why diabetes is so damaging to the heart — and how doctors might better predict and prevent those complications.

Researchers targeted one of diabetes' deadliest consequences: injury to the heart and blood vessels that nearly doubles the risk of major cardiovascular events. "Despite major advances in medical therapies and prevention strategies, the risk of cardiovascular complications in patients with diabetes remains substantially elevated," said Center Director **Mark Feinberg, M.D., FAHA.** "We wanted to understand why."

In the basic lab project, researchers honed in on powerful genetic regulators known as non-coding RNAs -- particularly in the endothelial cells that line blood vessels -- to understand how diabetes drives atherosclerosis and weakens recovery after a heart attack.

Using diabetic mouse models, they identified specific RNA signals that increase inflammation and impair blood vessel repair. Scientists hope that by tweaking those signals, they can dramatically slow plaque buildup, restore heart function, and develop entirely new RNA-based therapies.

Dr. Mark Feinberg

In the clinical-translational project, investigators harvested endothelial cells from patients with type 2 diabetes to map how diabetes ages blood vessels and test how widely used drugs like GLP-1 receptor agonists and SGLT2 inhibitors might reverse that damage. The results may help scientists pinpoint which therapies can restore vascular health and guide more precise treatment to prevent heart attacks.

In the population project, researchers analyzed data and biospecimens from more than 100,000 clinical trial participants to develop more accurate prediction scores for patients with diabetes. The research showed that by combining clinical factors with protein, RNA and genetic biomarkers, scientists could create "valuable tools to help refine risk for patients vulnerable to cardiovascular disease," Feinberg said.

He applauded the Heart Association for designing the SFRN with a synergistic basic-clinical-population study format. "It highlights how important a multidisciplinary team is and how well it works. It's exciting to see how some of the omic-based technologies can be used to help personalize therapy in ways we hadn't envisioned," he said.

"This SFRN allows for high-risk discovery efforts that drive deeper understanding of disease mechanisms and potential therapies. Without the Heart Association's funding, none of it would be possible."

Brigham & Women's Hospital Center

Dr. Chiadi Ndumele

Johns Hopkins University

Center Director: Chiadi Ndumele, M.D., Ph.D., FAHA

Fat isn't just stored energy. It's an active endocrine organ, sending out inflammatory signals that might help decide which people develop cardiometabolic disease and which do not.

Researchers at Johns Hopkins University delved deeper to understand why some obese patients remain metabolically stable for years while others tip into diabetes and heart disease, and whether adipokines -- proteins secreted by fat cells -- help drive that transition.

The basic science team studied mice engineered to mimic obesity and diabetes. The team found that two fat-derived hormones — adiponectin and resistin — appear to push the heart in opposite directions. The research showed these adipokines directly influence Dexras1, a stress-related protein, and AMPK, an energy regulator, triggering molecular changes that impair mitochondrial function and promote cardiac insulin resistance.

Center Director **Chiadi Ndumele, M.D., Ph.D., FAHA**, said the findings suggest these molecular shifts aren't just side effects of obesity and diabetes, but central drivers of heart failure, pointing to possible new targets for prediction and treatment.

In two related population projects, scientists learned that adipokines are key predictors of metabolic health in people with obesity. Pro-inflammatory adipokines, like leptin, were linked to worsening risk, while anti-inflammatory ones, such as adiponectin, predicted improvement or stability over time — showing who is likely to develop diabetes and who might stay healthier.

The studies confirmed diabetes speeds the shift from subtle cardiac changes to heart failure. The research also revealed new protein markers that flag early cardiac injury. Lower mitochondrial health tracked with higher risk, but weight loss — including through bariatric surgery — improved energy function and reduced heart damage.

Together, these study results may help doctors identify at-risk patients earlier and guide interventions that prevent or even reverse heart failure in people with obesity and diabetes.

"With this SFRN, the Heart Association is really helping to fill the gap at a critical moment when funding is so precarious. These projects don't just move forward science, they also set the foundation for future investigative work," Ndumele said.

New discoveries may be driven by the fellows who were trained during the SFRN.

"The shared training of fellows across the centers was an essential component of this," he said. "Cardiometabolic health and Type 2 diabetes are among the most pressing public health challenges of our time. By training the next generation of researchers, the Heart Association is supporting present and future work in this area."

Johns Hopkins University Center

New York University

Center Director: Ira Goldberg, M.D., FAHA

People with diabetes have long been known to face a much higher risk of heart disease—but the reason remains unclear.

At New York University, scientists set out to see whether the behavior of artery-clogging plaque might provide the answer.

Center Director **Ira Goldberg, M.D., FAHA**, said that while cholesterol-lowering treatments can reverse artery damage in most people, diabetes blocks this healing.

"All three of our projects asked the same question: What happens in people with diabetes versus those without when cholesterol is lowered? Why don't they get the same reduction in heart problems?"

The question carries particular weight for women, who tend to experience more harmful vascular effects from diabetes than men.

In the basic science project, researchers used mouse models to explore how diabetes affects artery repair. Normal mice with high cholesterol showed plaque regression and reduced inflammation when their cholesterol was lowered. Mice with diabetes, however, only saw about half that benefit. Their plaques remained inflamed, driven by a subgroup of white blood cells that failed to normalize, highlighting how diabetes interferes with the process of repair even when cholesterol levels improve.

In the parallel population project, scientists examined arterial plaques removed from human patients after aggressive cholesterol-lowering therapy. The results mirrored the mouse studies: people with diabetes had persistent abnormalities in certain white blood cells within their plaques, preventing full vascular repair.

Goldberg said the similarities between the studies suggest a shared mechanism that blocks artery healing in diabetes, pointing toward potential therapies that target these specific immune cells to restore normal plaque repair.

Dr. Ira Goldberg

In the clinical project, researchers studied people with and without type 2 diabetes, putting both groups through aggressive cholesterol reduction. While cholesterol dropped sharply, the usual blood markers -- white blood cell counts and platelet activity -- showed little change in people with diabetes, even though their vessels remained at risk.

The major finding, Goldberg said, is that traditional blood markers may not reflect what's actually happening in the blood vessels, highlighting the need for new ways to assess vascular health, like studying endothelial cells shed into the bloodstream.

Building on the SFRN studies, NYU scientists launched a new NIH-funded project extending the cholesterol-lowering research to people with type 1 diabetes. The goal is to pinpoint how different types of diabetes block artery repair.

"We never would've done this type of research without funding from the Heart Association, and we wouldn't have gotten the NIH grant either," he said. "I'd like to thank the Heart Association for fostering a community where people think and talk together to develop new therapies to reduce heart disease."

New York University Center

University of Iowa Center

University of Iowa

Center Director: E. Dale Abel, M.D., Ph.D., FAHA

Long before symptoms of heart disease emerge, microscopic signals silently damage the heart. To better understand, researchers at the University of Iowa took a closer look.

By tracking these signals in a wide range of places — mice, surgical patients and decades of blood samples — they uncovered early warning signs of cardiometabolic disease, as well as clues about how the heart might be protected.

"Even when you treat the diabetes or the blood pressure, some individuals still have an increased overall risk," said Center Director **E. Dale Abel, M.D., Ph.D., FAHA**. "We focused on understanding how other mediators from fat cells, liver, and muscle communicate with the heart and increase the risk of heart failure in people with diabetes."

Dr. E. Dale Abel

In the basic project, researchers bred mice to develop fatty liver disease without obesity, isolating what the liver releases into the bloodstream and how it affects the heart. They found that these stressed organs send out microscopic parcels known as extracellular vesicles, or "EVs," that carry proteins and genetic material that may disrupt heart function. This hidden biological dialogue might help explain why diabetes and obesity so often lead to heart failure.

In the clinical project, scientists followed people with obesity and prediabetes before and after bariatric surgery, using weight loss as a way to see how harmful biological signals changed. They analyzed fat tissue and blood to track EVs released by fat cells, and then they tested those vesicles on human heart and liver cells using "organ-on-a-plastic-chip" techniques.

The results showed that EVs from fat tissue altered cardiac function, linking diseased fat to heart damage. Advanced imaging also showed the heart's energy metabolism was impaired before bariatric surgery but rebounded after weight loss – a finding that suggests improving cardiometabolic health may restore the heart's fuel systems.

For the population project, researchers studied blood samples collected over more than 25 years to track how molecular signals evolved as people developed obesity, diabetes and heart disease. They measured over 100 proteins at multiple times and found early biological "fingerprints" of cardiometabolic risk. They also followed EVs and their RNA cargo, showing how these tiny messengers shifted as metabolic health declined.

"The challenges of cardiometabolic health are so big that no single group can figure it out," Abel said. "That's why it's so important to bring together a broad swath of experts in an SFRN like this to advance our knowledge and ultimately bring better treatments to our patients. The support of the Heart Association has been critical in developing the most exciting and compelling new ideas in this field."

THE FELLOWS: A CLOSER LOOK

The Fellowship Program

The fellowship program is an integral part of the Cardiometabolic Health and Type 2 Diabetes SFRN. It provided training and mentorship to a cohort of 20 postdoctoral fellows, resulting in new research initiatives, publications, and professional development within the field. This step is pivotal in shaping the next generation of innovative investigators.

Fellows were assigned to specific teams at each SFRN center. They forged relationships with scientists and mentors inside and outside of their centers as they conducted research on new ways to prevent and treat cardiometabolic disease. The fellows also advanced their careers by networking and presenting research at American Heart Association conferences and meetings.

"To be able to train and collaborate with the best cardiometabolic researchers in the world … it doesn't get much better than that," said Oversight Advisory Committee Chairperson Loren Wold, Ph.D., FAHA. "It's a truly exceptional experience."

"The fellows' impact is bidirectional. We learned as much from them as they did from us," said Brigham and Women's Hospital Center Director Mark Feinberg, M.D. "The trainees are the glue that integrated the program, not just within individual centers but across centers as well. The trainees are what really made the SFRN program so special."

Here are the stories of four of the fellows:

Anurag Jamaiyar, Ph.D.

Brigham and Women's Hospital

What began as a tricky project that ignited his curiosity about non-coding RNAs turned into an important discovery for Brigham and Women's Hospital fellow **Anurag Jamaiyar, Ph.D.**

Working with the center's basic science team, Jamaiyar uncovered a tiny molecule that could help hearts recover after a heart attack. The team found that miR-342-3p — a microRNA that helps regulate new blood vessel growth — fails to activate properly in hearts affected by diabetes. Without it, heart tissue is starved of oxygen and nutrients, slowing recovery.

Jamaiyar traced the molecule's effects in endothelial cells from both healthy and diabetic mouse hearts and found a hidden molecular switch that can jump-start healing. Boosting miR-342-3p in mice improved blood vessel growth, pointing to a potential new therapy for heart attack patients with diabetes. The findings may also help other conditions where poor blood flow slows recovery, offering hope for millions living with tissue damage.

The fellowship accelerated Jamaiyar's career as he published his research, presented it at conferences, and won major honors, including the 2023 Paul Dudley White International Scholar Award and the 2023 Arteriosclerosis, Thrombosis, and Vascular Biology Early Career Award. He said receiving the 2024 American Heart Association Career Development Award helped him secure a faculty position as an investigator and instructor at Brigham and Women's Hospital and Harvard Medical School.

Dr. Anurag Jamaiyar

In the future, he'd like to explore how non-coding RNAs influence gene expression in heart disease and related conditions. "I hope to translate discoveries made in my lab to the clinic so that a new generation of RNA therapeutics can alleviate the suffering of patients," he said.

Jamaiyar praised Mark Feinberg for his mentorship, saying that "his guidance and insights were crucial to the success of this project. As I was new to the world of non-coding RNAs, Dr. Feinberg introduced me to a range of new techniques, assays and resources to help ease me into this exciting area of research."

And he lauded the Heart Association for designing a well-rounded fellowship that helped him refine his skills in writing, presentations and grant proposals. "I'd recommend this SFRN to future colleagues," he said. "It has a transformative effect on early-career scientists."

Bige Ozkan, M.D., ScM

Johns Hopkins University

The research of **Bige Ozkan, M.D.**, is giving new meaning to the phrase "listen to your body."

As a fellow in Johns Hopkins University's SFRN center team, Ozkan showed that two proteins in the blood, adiponectin and leptin, can indicate whether someone's metabolism is likely to stay healthy or tip toward risk. The first author in a paper published in The Journal of Clinical Endocrinology & Metabolism, Ozkan analyzed data from more than 8,000 adults collected over six years to track changes in the body's ability to manage sugar and fat efficiently.

The team discovered that higher levels of adiponectin were linked to staying healthy or even improving from metabolic risk, while higher leptin made slipping into unhealthy states more likely.

The findings highlight how subtle chemical signals in the blood can forecast long-term heart and metabolic health. "This work helps us identify biological pathways that could be targeted to reduce the risk of cardiovascular problems before they develop," she said.

Dr. Bige Ozkan

In the future, Ozkan plans to focus her research on cardiometabolic disease and heart failure to help understand the link between obesity, metabolic health, and cardiovascular disease, especially in high-risk populations. "Ultimately, I hope to contribute to both improving patient care and training the next generation of physicians and scientists in this field," she said.

She thanked her fellowship mentor **Chiadi Ndumele, M.D., Ph.D., FAHA** for "invaluable guidance" and praised **Elizabeth Selvin, Ph.D., MPH** and **Josef Coresh, M.D., Ph.D., MHS**, "whose mentorship in population science and rigorous study design has been instrumental in shaping my approach to clinical research."

Ozkan described the fellowship as "an exceptional training environment" that sharpened her skills in epidemiologic research and big-data analysis and taught her to ask important research questions.

"The American Heart Association SFRN fellowship helped me expand my professional network through collaborations with investigators across institutions," she said. "It gave me an invaluable head start in building my career as a physician-scientist dedicated to improving cardiovascular health through research and patient care."

Natalia Eberhardt, Ph.D.

New York University

For decades, doctors mostly blamed heart disease on cholesterol clogging the arteries. But New York University center fellow **Natalia Eberhardt, Ph.D.**, was looking somewhere else: the immune system.

Working with her center's population project team, Eberhardt studied how diabetes changes certain white blood cells inside the fatty plaques that build up in arteries and restrict blood flow, triggering heart attacks.

By examining immune cells taken from plaques removed during artery-clearing surgery, Eberhardt and her fellow researchers found that a white blood cell, CD8 T, could become stuck in an overactive state in people with Type 2 diabetes. Instead of calming inflammation and helping blood vessels heal, the cells continued to send signals that kept arteries inflamed.

Her findings added to growing evidence that heart disease may be driven not just by cholesterol buildup but also by chronic inflammation. "This framework could help health professionals better identify patients at higher risk of disease progression and guide the development of more precise strategies aimed at restoring immune balance, rather than broadly suppressing inflammation," she said.

Eberhardt thanked her primary mentor, Chiara Giannarelli, M.D., Ph.D., FAHA, for teaching her to study cardiovascular disease using an immunology-based approach that combines human tissue analysis with mechanistic insight. She credited Edward Fisher, M.D., Ph.D., FAHA for providing expertise in mouse models of diabetes and atherosclerosis. And, she said, she got tremendous support from Jeffrey Berger, M.D., FAHA, Ira Goldberg, M.D., FAHA and the team behind CHORD, NYU's study of cholesterol lowering and diabetes risk.

Dr. Natalia Eberhardt

"The Heart Association has designed an exceptional collaborative network that challenged me to think differently," she said. "What made the SFRN unique for me was the regular interaction between investigators studying the same disease from different angles. That environment accelerated my growth in a way that wouldn't have happened within a single-lab structure. It's been incredibly valuable for my career."

Currently a senior postdoctoral fellow in cardiovascular immunology, Eberhardt hopes to build an independent research program to study how aging of the immune system and chronic inflammation contribute to heart disease, especially among people with diabetes.

"My goal is to identify actionable pathways that can be translated into more precise, patient-centered therapies," she said. "Ultimately, I want my work to help close the gap between mechanistic immunology and real-world cardiovascular outcomes."

Andrew Perry, M.D.

University of Iowa

Most physicians navigate a maze of career choices: Which specialty to pursue? Where to do a residency? Which mentors to invest in?

But for **Andrew Perry, M.D.**, one choice rose above the rest.

"Participating in the Heart Association's SFRN was the best decision of my career," he said.

Working with the University of Iowa population team, Perry studied whether molecules in the blood could reveal hidden mechanisms behind obesity, diabetes, fatty liver, and heart failure. Drawing on decades of stored NIH-funded samples, he used machine learning to trace patterns over time, linking molecular fingerprints to early cardiometabolic risk.

He and his fellow researchers honed in on extracellular vesicles, or EVs -- microscopic parcels released by fat, liver and muscle that can disrupt heart function. Tracking these signals across more than 25 years, Perry and his teammates identified novel molecules that mark disease progression long before symptoms appear, highlighting potential targets for testing and treatment.

Dr. Andrew Perry

Looking ahead, Perry plans to focus on recovery in heart failure and wants to use new "omics" technologies to find out why some patients improve clinically, and others don't.

"I'd like to ultimately identify a novel pathway that is intervenable to improve clinical outcomes for patients," he said.

He praised his mentor, Ravi Shah, M.D., FAHA, for teaching him how to tackle multi-"omic" analyses. Perry also learned new skills from the SFRN's quarterly career talks and grant workshops.

But in the end, the fellowship was more than just a learning opportunity. It was a career launchpad.

As a result of the SFRN, Perry secured his first major grant, a K23 from the NHLBI, and earned a seat on the Heart Association's Scientific Committee on Obesity. He also landed a physician-scientist position as assistant professor of medicine at Vanderbilt University Medical Center.

"It was a great environment with supportive mentors and ample resources," he said of the fellowship. "It really helped me build momentum in an investigative career."

COLLABORATIONS

Collaboration has long been an important aspiration for the SFRN, and in the current cycle it has taken on an even more central role.

For the first time, the Heart Association reserved funding for a shared project developed collectively by all four centers.

"It was a really strategic move by the American Heart Association to leverage everyone's different expertise," said Oversight Advisory Committee Chairperson Loren Wold, Ph.D., FAHA. "It brought all the centers together at the same table with all of their different strengths to ask questions that could not have otherwise been asked."

Brigham and Women's Hospital Center Director Mark Feinberg, M.D., FAHA, said the centers aligned their approaches to analyzing genetic data and pooled clinical proteomics studies, allowing biomarkers discovered at one center to be tested and validated in patient populations across the network.

Researchers didn't just coordinate experiments — they coordinated the mouse menu, coming up with a multi-institution meal plan for genetically engineered mice.

"It turns out we all were using different diets for inducing diabetes and insulin resistance," Feinberg explained. "So we harmonized our animal models and standardized the diet across the centers so we could compare apples-to-apples for different findings that impact disease progression, whether it's in atherosclerosis or myocardial injury."

In another collaborative effort, scientists across the SFRN began isolating endothelial cells from patients using a shared approach. The project allowed teams at New York University and Brigham and Women's Hospital to compare methods and results and contribute samples to a lipid-lowering clinical trial.

These were just a few examples of the many productive collaborations that emerged as scientists across the network joined forces.

"Science really advances when you have a community getting together, talking, critiquing, and exchanging ideas," said New York University Center Director Ira Goldberg, M.D., FAHA, "The collaborative project really helped all four centers refine what we were doing and spark a cross-pollination of ideas."

CONCLUSION

Cardiometabolic disease, a web of conditions involving the heart, blood vessels and metabolism, has become widespread in the U.S., affecting at least three out of four adults. Among the most serious is Type 2 Diabetes, which affects about 36 million Americans and roughly doubles the risk of heart attack, stroke and other cardiovascular complications.

While the problem has been known for years, "we're still in the infancy of truly understanding how heart disease develops related to diabetes," said Oversight Advisory Committee Chairperson **Loren Wold, Ph.D., FAHA**.

The Cardiometabolic Health & Type 2 Diabetes SFRN has helped unlock some of those mysteries while providing rigorous training to the next generation of researchers, Wold said.

"With networks like this, the Heart Association continues to be a beacon of hope for investigators dedicated to doing exceptional science to improve cardiovascular health."

The Heart Association launched its first SFRN in 2014 and has since created 18 SFRNs. In addition to Cardiometabolic Health and Type 2 Diabetes, other networks have focused on Atrial Fibrillation, Arrhythmias and Sudden Cardiac Death, Prevention, Hypertension, Disparities in CVD & Stroke, Go Red for Women, Heart Failure, Obesity, Children's Health, Vascular Disease, Health Technologies & Innovation, Cardio-Oncology, Science of Diversity in Clinical Trials, Biological Impact of Chronic Psychosocial Stress, Role of Inflammation in Cardiovascular Health, Cardiovascular Kidney Metabolic Syndrome: Heterogeneity in Women, and Earlier Detection and Delaying Progression of Valvular Heart Disease.

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