Team Science
American Heart Association’s Hypertension Strategically Focused Research Network Experience


ABSTRACT: In 2015, the American Heart Association awarded 4-year funding for a Strategically Focused Research Network focused on hypertension composed of 4 Centers: Cincinnati Children’s Hospital, Medical College of Wisconsin, University of Alabama at Birmingham, and University of Iowa. Each center proposed 3 integrated (basic, clinical, and population science) projects around a single area of focus relevant to hypertension. Along with scientific progress, the American Heart Association put a significant emphasis on training of next-generation hypertension researchers by sponsoring 3 postdoctoral fellows per center over 4 years. With the center projects being spread across the continuum of basic, clinical, and population sciences, postdoctoral fellows were expected to garner experience in various types of research methodologies. The American Heart Association also provided a number of leadership development opportunities for fellows and investigators in these centers. In addition, collaboration was highly encouraged among the centers (both within and outside the network) with the American Heart Association providing multiple opportunities for meeting and expanding associations. The area of focus for the Cincinnati Children’s Hospital Center was hypertension and target organ damage in children utilizing ambulatory blood pressure measurements. The Medical College of Wisconsin Center focused on epigenetic modifications and their role in pathogenesis of hypertension using human and animal studies. The University of Alabama at Birmingham Center’s areas of research were diurnal blood pressure patterns and clock genes. The University of Iowa Center evaluated copeptin as a possible early biomarker for preeclampsia and vascular endothelial function during pregnancy. In this review, challenges faced and successes achieved by the investigators of each of the centers are presented.

Key Words: biomarkers • hospitals • hypertension • interdisciplinary research • preeclampsia
from bench to bedside to community-based research. The AHA also provided a number of leadership development opportunities for fellows and investigators in these centers. In addition, collaboration was highly encouraged among the centers (both within and outside network) with AHA providing multiple avenues for meeting and expanding associations. Each center’s investigators and fellows were also required to present work-in-progress data to investigators from other centers, as well as to the oversight committee at least annually throughout the award period, receive feedback, and consider suggestions received.

The area of focus for the CCH Center was hypertension and target organ damage in children and adolescents utilizing ambulatory blood pressure measurements as a tool to measure blood pressure (BP). The MCW Center focused on epigenetic modifications (DNA methylation changes) and their role in pathogenesis of hypertension using human and animal studies. The UAB Center’s areas of research were diurnal BP patterns and clock genes. The UI Center evaluated copeptin as a possible early biomarker for preeclampsia and vascular endothelial function during pregnancy. This review was commissioned to describe the science from research projects proposed by each center, as well as successes and challenges experienced in implementation of proposed projects, fellowship training, and development of collaborations.

**OUR EXPERIENCE**

**CCH Center**

**Overall Hypotheses and Goals**

To examine the concept that hypertensive cardiovascular injury emerges during early stages of primary hypertension, 3 projects were designed by the CCH Center (the SHIP AHOY [Systolic Hypertension in Pediatrics - Adult Hypertension Onset in Youth] study). Nearly 400 adolescents were enrolled at 3 BP thresholds: normal (systolic BP, <75th percentile), mid-risk (systolic BP, >75th but <90th percentile) and high-risk (systolic BP, >90th percentile) categories (Figure 1). Investigators hypothesized that the prevalence of target organ damage (left ventricular mass, pulse wave velocity, urinary albumin excretion, and cognitive function) would be greater at higher levels of BP (population science project). In addition, it was hypothesized that (sustained) 24-hour ambulatory hypertension and multiple metabolic syndrome risk factors would predict the presence of target organ damage (clinical science project). The third part of the study (basic science) investigated epigenetic changes that influence the development of target organ damage in youth with hypertension.

**Successes and Challenges**

Success of the CCH center was rooted in its ability to develop multiple collaborating centers to ensure adequate enrollment since pediatric hypertension is not common. This multicenter collaboration was effective due to previous partnerships among the PIs as part of the International Pediatric Hypertension Association. Weekly web-based calls ensured close communication between various centers. Center PI’s coordinator had weekly contacts with other site coordinators facilitating recruitment and timely data transfer. Fellowship recruitment was enhanced by a strong preexisting pediatric cardiology fellowship program resulting in a diverse group of fellows including a pediatric cardiologist, a pediatric nephrologist, and an investigator with expertise in laboratory science (Table 1). A multidisciplinary group of topic experts (cardiology, nephrology, genetics, psychology, and statistics) provided didactic lectures in the population, clinical, and basic science areas to CCH and other SFRN fellows. The SHIP AHOY

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**Nonstandard Abbreviations and Acronyms**

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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<td>BP</td>
<td>blood pressure</td>
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<td>CCH</td>
<td>Cincinnati Children’s Hospital</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>MCW</td>
<td>Medical College of Wisconsin</td>
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<td>PI</td>
<td>principal investigator</td>
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<td>RGS2</td>
<td>regulator of G-protein signaling-2</td>
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<td>SFRN</td>
<td>Strategically Focused Research Network</td>
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<td>UAB</td>
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study included cognitive assessments of teens using face-to-face interviews and questionnaires. These assessments required training of nonpsychologists, development of a standardized process for certification, regular quality assurance checks, and follow-ups to specific site examiners when questions arose. The center was able to ensure the quality of cognitive data through these rigorous processes. These methods will form a blueprint for upcoming studies that include cognitive assessments in multicenter studies.

CCH was also successful in initiating several new collaborations banking on preexisting connections with hypertension investigators in other centers: (1) The UI Center’s project on preeclampsia was the impetus to gather data on maternal preeclampsia from subjects enrolled in the SHIP AHOY study. Additional blood was collected to assess copeptin levels from the participants. Analyses were performed to determine whether maternal preeclampsia or copeptin levels in teens influenced BP levels or target organ damage. No relationship was discovered between maternal preeclampsia or copeptin levels in teens with teen BP levels or hypertension; (2) CCH also developed collaboration with the MCW Center and collected and isolated T cells using the MCW protocol on 45 subjects. However, neither site had funding for analysis to explore the epigenetics of salt sensitivity in youth; and (3) SFRN renewal grant was submitted with investigators from Disparities in Cardiovascular Disease (CVD) SFRN Center at the Northwestern University in Chicago to examine the relationship between fibroblast growth factor 23 and left ventricular mass in youth. This was not funded, but future applications for the National Institutes of Health funding are in preparation.

Main challenges were focused around recruitment. Nearly 50% of new subjects deemed hypertensive at the pediatrician’s office and referred for enrollment were normotensive when BP was measured appropriately in the research setting. For this reason, investigators had to add additional recruitment sites. Additional difficulties were faced by the CCH Center in developing new and ongoing collaborations. Although collaboration with UI Center proceeded smoothly, the results were negative, and the collaboration did not continue. A collaboration with the UAB Center to develop ambulatory BP monitoring arena further was contemplated, but this did not proceed due to time constraints placed on the fellows. Due to funding issues, collaboration with the MCW Center could not be pursued further. The CCH Center also faced challenges with the basic science project because it had to be delayed until sufficient samples were collected for processing. Rapid changes in the fields of genetics, bioinformatics, and systems-based molecular biology necessitated changes in alteration to original candidate gene-based approach to genome-wide gene expression products.

Future Directions for the Center
Preliminary findings from the epigenetic studies will be used to apply for funding for translational studies.
including collecting new samples from the established cohort, culturing cardiomyocytes from participant inducible pluripotent stem cells, and testing hypotheses in animal studies. CCH also plans to pursue funding to evaluate the relationship between Fibroblast Growth Factor 23 and target organ damage.

**MCW Center**

**Overall Hypotheses and Goals**

The objective of the MCW Center program was to carry out a systematic investigation of the relevance of genome-wide DNA methylation patterns to hypertension. Hypertension has long been considered a result of interactions between one’s genetic background and environmental factors, including diet and other lifestyle choices.\(^1\) One way the environment may interact with the genome and influence organismal physiology and disease is through epigenetic modifications, which are molecular changes to the DNA (unrelated to its sequence) that lead to changes in gene expression.\(^2,3\) Overall hypothesis was that dietary salt intake, maternal dietary exposures, and other lifestyle factors cause genome-wide changes in DNA methylation (a type of epigenetic modification), which contribute to the development of hypertension and can be used as predictive or diagnostic markers of hypertension and related diseases (Figure 2). All 3 projects analyzed DNA methylation at near genome-wide scale using the technology of reduced representation bisulfite sequencing as described previously.\(^4-5\) Basic and clinical science projects used immune cells for methylation analyses.

**Successes and Challenges**

MCW’s SFRN catalyzed the expansion of Team Science by promoting the interaction among basic scientists, clinical investigators, epidemiologists, bioinformatics experts, and genomic scientists to design studies and obtain and analyze data. Several published articles were supported by this SFRN with several additional abstracts containing data that we plan to publish in the future.\(^6-13\) Investigators were able to adhere to the hypotheses proposed with no major changes due to innovative ideas in implementation of the projects. In the basic science project, changes were observed in DNA methylation and gene expression in T lymphocytes (T cells) of Dahl salt-sensitive rats fed different diets,\(^6\) providing new insight into the mechanisms by which immune mechanisms amplify salt-sensitive hypertension and renal damage. The clinical project started with de novo recruitment of 150 pairs of identical twins in collaboration with the Michigan State University Twin Registry. They were phenotyped and sequenced for differential methylation in T cells among BP concordant and discordant twins (publication pending). In addition, salt sensitivity was assessed in 50 human subjects using a 2-week 1200-mg low-sodium diet and completed methylation analyses of T cells (pending publication). As part of the population study, a 10-year follow-up database of 1000 Black people was created and is the basis of multiple ongoing observations. Whole-blood DNA methylation sequencing of ≈500 subjects was completed. It was observed that stored DNA samples (as long as 20 years at 4 °C) are suitable for comparative studies of DNA methylation.\(^8\) In addition, it was observed that in Black people, 24-hour BP monitoring provides limited added value as a predictor of cardiovascular/renal disease events.\(^10\) SFRN enabled postdoctoral fellows to participate in multiple types of research and learn how basic and clinical studies are conducted and strengths and limitations of each (Table 1). In addition to specific successes in each of the projects, The MCW Center also made critical methodological advances in the realm of methylation sequencing and analyses.\(^14\)

The MCW Center faced challenges in the arena of subject recruitment as expected with any clinical study with complex inclusion criteria and cost overruns. It was realized that despite having access to a database of twins (from the Michigan State University), recruitment was still difficult and costly. The award duration was short (4 years), given the scope of the projects and the delays in start of de novo projects after acquisition of funding. Data analyses took longer than expected as methylation data analysis is new and required innovative approaches; however, The MCW Center's strength was a strong bioinformatics and statistics team, which allowed robust data analyses. It was challenging to recruit clinical fellows to the postdoctoral fellowship; however, in the end, the MCW Center was able to be successful in training qualified fellows who provided the much needed complimentary expertise.

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**Figure 2.** Schematic describing the Medical College of Wisconsin’s Hypertension Strategically Focused Research Network Center’s investigators hypothesized that dietary salt intake, maternal dietary exposures, and other lifestyle interactions cause genome-wide changes in DNA methylation (type of epigenetic modification), which contribute to the development of hypertension (HTN) and can be used as predictive or diagnostic markers of HTN and related diseases.

CVD indicates cardiovascular disease.
**Future Directions for the Center**

Of equal or perhaps greater value than scientific advances, the SFRN facilitated continued collaboration between basic and clinical scientists and opened up translational opportunities that will be fruitful in future basic science projects leading to an important new area to pursue—the microbiome. Initial work in that field has been presented in abstract form (FASEB J. 2019;33[suppl 1]:866.9. Abstract) and has presently been submitted for publication. The Clinical Science project's success in assessing salt sensitivity established a track record and will be the basis of new project that will be submitted for future funding. Investigators believe that some of the best work from the SFRN is still to come as the work from the clinical and population projects comes to completion. It is hoped that correlates can be found between the data in the animal models and the humans and interrogate those genes to understand the mechanistic basis of human disease.

**UAB Center**

**Overall Hypotheses and Goals**

The UAB SFRN hypertension center was designed to generate new evidence on the role of diurnal BP on CVD risk. Investigators proposed that an abnormal diurnal BP pattern (ie, nocturnal hypertension and a nondipping BP pattern) is an underdetected silent CVD risk factor, its underlying mechanisms can be identified through basic and clinical research, and these patterns can be diagnosed and treated cost-effectively at the population level. Therefore, the exploration of the etiologies and complications of abnormal diurnal BP patterns was the central theme of the UAB Center (Figure 3). Their integrated program of research included (1) a population science project that generated data on the burden of nocturnal hypertension and nondipping BP, (2) a clinical science project of a randomized crossover study designed to determine whether dietary sodium restriction reduces nocturnal BP and restores normal BP dipping through improvements in sleep-disordered breathing, and (3) a series of basic science studies that further examined novel salt-dependent mechanisms promoting renal microvascular dysfunction, which in turn leads to dysregulation of diurnal sodium handling and BP. Three outstanding early-stage investigators were mentored who gained transdisciplinary population, clinical, and basic science training (Table 1).

**Successes and Challenges**

The successes of the UAB SFRN resulted from the long-standing collaborations between basic, clinical, and population hypertension research at UAB. When the SFRN was initiated in 2015, there was a strong foundation including a T32 that is currently in its 40th year of continuous funding and the UAB Vascular Biology and Hypertension Symposium, which has been held annually since 1989. In 2019 and 2020, this symposium received funding from the National Heart, Lung, and Blood Institute through an R13 grant. The population science project published findings on (1) the prevalence of out-of-office BP phenotypes according to the 2017 Hypertension Guidelines, (2) the association between nocturnal BP and CVD risk among Black people, (3) the association of health behaviors with nocturnal hypertension, and (4) the estimated prevalence of nocturnal hypertension among US adults. The clinical science project had 53 participants successfully complete all phases of their dietary intervention crossover study by the end of 2019. Preliminary analyses of 24-hour urinary sodium excretion demonstrated that participants were adherent to their assigned diets (6 versus 1.5 g of sodium/day) without evidence of any carryover effects. Given these positive results, analyses are being conducted to determine the effect of dietary sodium intake on severity of sleep apnea and diurnal BP levels. The basic science project has focused on delineating novel high salt–dependent pathways (histone deacetylases and the E3 ubiquitin protein ligase, RFWD2) that are regulated by clock genes. The clinical and basic science teams collaborated to publish a study defining a novel method to integrate circadian measurements with peripheral clock genes in humans and a review titled “Circadian Regulation of BP: of Mice and Men.” Furthermore, the clinical and population science teams collaborated to publish a manuscript on the association of sleep characteristics with nocturnal
hypertension and nondipping BP. In addition, the UAB SFRN collaborated with the MCW SFRN to publish data on clinic and ambulatory BP among Black people in the Jackson Heart Study.

Despite the successes of the UAB SFRN, many challenges were experienced over the funding period. Only 835 participants completed ambulatory BP monitoring as part of the population science project. However, investigators were able to supplement these data with ambulatory BP monitoring recordings from other studies. The clinical science project was delayed due to staffing issues. However, during no-cost extension period, they were able to successfully complete the study, and results are currently being prepared for publication. The basic science project also had staffing issues that resolved with collaborations within the clinical and population teams to assist in data analyses. Finally, personnel turnover including an investigator who retired and another who took a leadership position at another institution resulted in minor delays. Fortunately, these investigators have remained engaged with the center and the mentoring of the fellows.

Future Directions for the Center
The UAB center was refunded by the AHA for a study focused on whether reduced sodium intake is associated with higher levels of short-chain fatty acids (an endogenous histone deacetylase inhibitor) and lower levels of oxidative stress. Additionally, the center has received funding as a University-Wide Interdisciplinary Research Center and the Hypertension Research Center was designated as a center by the University of Alabama Board of Trustees. Dr. S. Justin Thomas—the first UAB SFRN fellow and now a faculty member—is a founding codirector of the UAB Sleep and Circadian Research Core. This core supports research focused on time-restricted feeding, timing of sodium intake, and sleep patterns as they relate to BP and other cardiometabolic risk factors. Ongoing National Institutes of Health–funded and AHA-funded studies for the UAB SFRN investigators are focused on time-restricted feeding, timing of sodium intake, testing home BP measurement devices to assess BP during sleep, an ambulatory BP monitoring pooling project, home BP monitoring in older adults, and central and peripheral mechanisms underlying nondipping BP in Black adults.

UI Center
Overall Hypotheses and Goals
The UI SFRN Hypertension Center was designed to investigate the involvement of the neurohypophyseal hormone arginine vasopressin and its metabolic products in the prediction, diagnosis, modeling, and pathogenesis of the prevalent pregnancy-related hypertensive disorder preeclampsia, which is associated with immediate and long-term maternal-fetal morbidity and mortality (Figure 4). It was previously demonstrated that arginine vasopressin release is robustly predictive of the development of human preeclampsia and successfully models the disease in mice. These early findings initiated the center’s future studies in both mice and humans.

Successes and Challenges
The successes of the Iowa Center predominantly arose from existing, organic, and close collaborations of the center director and the individual study PIs. Goal-oriented project focus and group structure, multiple partially overlapping, regularly occurring (ie, weekly) cross-project group meetings, preexisting shared resources (ie, pathology and phenotyping cores, biobanks, and clinical research support teams), and complementary cross-disciplinary areas of expertise helped accelerate the projects. A key resource that propelled the translational nature of the basic, clinical, and population studies was the Iowa Maternal Fetal Tissue Bank as the central machinery in which (1) pregnant women and their children are enrolled, (2) biomaterials are collected, and (3) clinical data are curated to improve our knowledge of pregnancy and its effects on maternal and child health. This machinery has developed a national cohort of perinatal clinics and practices that are a rich resource of clinical data and biological samples. Early mechanistic and biomarker work in plasma and urine from this cohort has resulted in multiple patents that can easily be translated to clinical practice. This work resulted in many new mechanistic insights in the pleiotropic vascular and immune role of arginine vasopressin in the development of preeclampsia. Additional unanticipated extensions of this work have implicated RGS2 (regulator of G-protein signaling-2; a regulator of common immunovascular hormones such as angiotensin, endothelin-1, and arginine vasopressin) in preeclampsia and its vascular dysfunction. In addition, a potential novel hemodynamic biomarker, short-term beat-to-beat BP variability,
that is prospectively associated with the development of preeclampsia and elevated arterial stiffness in the first trimester was discovered. Further, this study also highlighted that vascular dysfunction can easily be detected as early as the first trimester long before the development of the other clinical signs and symptoms.

While the UI Center has established many successful collaborations, a major challenge to the progression of this translational work at the national level is the delay inherent in building collaborative sites with no research architecture. Using the lessons learned from building the system associated within this SFRN, the team has been successful in obtaining National Institutes of Health funding to expand this cohort to build research architecture using teleresearch technologies in research-void environments.

**Future Directions for the Center**

The Iowa Center’s current focus is upon exploring the mechanisms of preeclampsia that lead to future CVD, cognitive impairment in the mother and offspring, and further immunologic mechanisms underpinning this disease. The AHA has funded an ongoing collaboration between elements of the now-former centers at UI and Magee Women’s Research Institute to evaluate novel RGS2-related preeclampsia immunovascular mechanisms leading to future hypertension, including masked hypertension identified with home BP monitoring, and CVD. Ongoing National Institutes of Health Research Project Grant R01 and AHA Innovative Project and Established Investigator Awards to individual members of the team support these continued efforts in identifying novel therapeutic targets for preeclampsia and its downstream cardiovascular morbidity and mortality.

**STRENGTHS AND FUTURE OPPORTUNITIES FOR SFRNS**

SFRNs are an unprecedented effort by AHA to bring team science to the forefront to solve big challenging health care problems that require multiple disciplines to work together. By mandating that each center proposes projects spanning basic, clinical, and population sciences, it facilitated interdisciplinary and interprofessional investigator teams to collaborate. Based on experiences of the PIs, intracenter collaborations were highly successful among the PIs and center directors. However, intercenter collaborations were faced with difficulties due to lack of specific funding to develop and continue projects initiated. While there are examples of AHA-funded collaborative efforts in the SFRN hypertension like the Iowa (hypertension) and Magee (Go Red For Women) AHA Strategic Collaborative Grant, this mechanism was meant for all existing SFRNs (Table 2). SFRN-related projects have been productive as seen by the addition of significant publications to the literature that cover a wide variety of study types including epidemiological, clinical, translational, and basic science studies (Table 2). In addition, the duration of the award was just 4 years and was felt to be too short for many of the projects to be completed and analyzed. It was difficult to continue many promising projects due to lack of opportunities to renew the funding.

Development of next-generation hypertension researchers was a key priority for AHA. Overall, this objective was successful with training of 12 outstanding physicians and scientists interested in the field of hypertension. Plenty of mentorship opportunities were facilitated by the

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<th>HTN SFRN Center</th>
<th>Collaborating Institution/Center</th>
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<tr>
<td>Iowa HTN SFRN</td>
<td>Magee Go Red For Women SFRN</td>
<td>Mechanisms for Early and Late Postpartum Hypertension in Human Preeclampsia</td>
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<td>Improving the Detection of Masked Hypertension: Analysis of Pooled Population- and Community-Based Studies</td>
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<td>Central and Peripheral Circadian Mechanisms Underlying Non-Dipping Blood Pressure in Blacks</td>
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Referenced publications: [231,13,1820134-47]. AHA indicates American Heart Association; AHA PREDICTV, AHA Preeclampsia Early Determination for Intervention Cure, & Therapeutics by Vasopressin; HTN, hypertension; iELEVATE, Improving Women’s and Children’s Health via Biobanking and Electronic Registry; Iowa ICTS, Iowa Institute for Clinical and Translational Science; NCATS, National Center for Advancing Translational Sciences; NHLBI, National Heart, Lung, and Blood Institute; SFRN, Strategically Focused Research Network; and UAB, University of Alabama at Birmingham.
AHA via SFRN-specific programs at annual hypertension meetings and leadership academy meetings. These programs were important strengths of the program since it brought together the trainees at national meetings and provided special forums to network and present their work. Although trainees were always encouraged to attend the national meetings, they are often lost in a sea of more established investigators and do not have the opportunity to meet and get to know one another. Smaller settings organized by the AHA for the center investigators and fellows was of immense use. Some parts of the SFRN program for fellows such as grant and manuscript writing and ethics workshops were of less importance since there was much redundancy with institutional programs.

To improve future SFRNs, we recommend the following specific steps: (1) more robust opportunities be provided for continuation of the work that was initiated in the SFRNs via additional renewal mechanisms; (2) separate funding to promote collaborations between SFRN centers might improve successes of intercenter collaborations. As an example, 1 SFRN, Go Red For Women, had additional research funding available for promoting collaborative projects among the Go Red For Women SFRN centers, and perhaps this model could be followed for future SFRNs. (3) Specific future funding mechanisms for SFRN trainees could encourage trainees to remain in science and pursue their own future research, this would be particularly helpful to keep clinical trainees in science.

The SFRN hypertension represents a success for the innovative comprehensive multicenter network approach for themed research by facilitating investigators to maximize collaboration and interdisciplinary work. Further development of the SFRN mechanism with more resources will allow AHA encourage and own the advancement and innovation of CVD research through this innovative program.

ARTICLE INFORMATION

Affiliations

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REFERENCES


