NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION, INC.

DNA

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Focus on Research

A gut feeling about microbiome research

Most people would consider the inside of the large intestine to be unpleasant.

Yet amid the food fragments that are about to become waste, there is a robust ecosystem of trillions of bacteria, viruses, fungi, and other organisms that impact our health within the digestive system and beyond.

For physician-scientist Dr. Renuka Nayak, the microscopic world of the gut microbiome is an untapped treasure trove for research.

Scientists know that gut microbiota helps harness energy from the foods we eat, synthesize essential vitamins, and even produce metabolites critical to the immune system. The metabolic mechanisms of the gut microbiome, however, are largely unknown. Moreover, there are up to 1,000 species of bacteria in the gut microbiome, but for 50 percent of them, their role and activity in the body remain to be discovered.

Nayak, an NCIRE-supported scientist, strives to uncover these phenomenons and their individual parts. Her laboratory team at the San Francisco VA Health Care System (SFVAHCS) uses an innovative combination of patient specimens, microbiology, next generation sequencing, and gnotobiotic mouse models to understand how our microbiome influences health and disease.

"I have been in awe of the complexity of the microbiome, and we have the opportunity to dissect out microbial mechanisms and test them in a reductionist way (in a petri dish) as well as in the host (in mice and humans)," said Nayak.

Renuka Nayak, MD, PhD

Associate Professor In Residence,
Medicine (Rheumatology)
University of California, San Francisco

Staff Physician and Principal Investigator
San Francisco VA Health Care System

Nayak's unique scientific background—degrees in biology, computer science, and genomics—combines with her clinical devotion to treating patients with rheumatic disease.

"Microbiome research is highly interdisciplinary as well, which makes it fun," she said. "You must work closely with others to drive the research. You get to learn from others and share your knowledge."

What drives her lab is the great potential to apply microbiome research to personalized treatment, especially for those who suffer from diseases in which the immune system goes awry and attacks the body's tissues.

"While mounting evidence suggests that the microbiome may impact the onset, progression, and treatment of disease in humans, essentially none of our current therapies intentionally target the microbiota," said Nayak. "Thus, we have an opportunity to develop substantively novel therapies if we elucidate the mechanisms by which the human gut microbiota contributes to the treatment of autoimmune disease."

Microbiome impact on rheumatoid arthritis treatment

One of those autoimmune diseases is rheumatoid arthritis (RA), a debilitating and painful disorder that damages the joints in the hands, wrists, and knees. It can also affect the skin, eyes, lungs, heart, and blood vessels. In the U.S., some 1.5 million people—mostly women (with a female-to-male ratio of three to one)—suffer from RA, according to the Centers for Disease Control and Prevention.

As with other autoimmune disorders, RA can be treated with oral medications that interact with gut microbes. One such treatment—an immunosuppressive drug, oral methotrexate—is a first-line therapy for RA.

Doctors, however, employ a trial-and-error approach when prescribing the treatment, and it is ineffective in 50 to 70 percent of patients. Furthermore, the drug takes three months to be effective, so it will take at least that long to figure out if methotrexate will work for a patient. "A major drawback is that precious time is lost in controlling the disease and continued inflammation could lead to worsening joint destruction," said Nayak.

"About two-thirds of RA patients will need more than just methotrexate," she said. "It would be great to know from day one whether they will respond to methotrexate or not. Neither the patient nor I want three months of suffering or waiting to figure out if a drug will be effective."

"This is something that precision medicine strategies strive to figure out," she said.

Nayak is now deciphering the underlying mechanisms of how methotrexate acts on the microbiota. Learning how it alleviates RA may lead to the identification and targeting of microbes, their proteins, or metabolites that contribute to or exacerbate autoimmunity.

"Instead of broadly immunosuppressing patients, we can develop therapies targeting facets of the microbiota that contribute to disease," she said.

"Examples of therapies that target the microbiome include diet, fecal microbiota transplant, probiotics, antibiotics, small molecules that target microbial proteins, vaccines that target specific microbes, clustered regularly interspaced short palindromic repeats (CRISPR) editing of microbial genes, and phage therapy (viruses that kill specific bacteria)," said Nayak.

"There is not enough data at this time to know if these types of therapies will benefit our patients, but there is a lot of research underway to investigate this," she said. "There is still a lot of foundational knowledge that we are learning about the microbiome, which is incredibly complex, and I think efforts to understand the basic biology as well as human microbiome biology will be key in making therapeutic advances."

Patients inspire lab research

Researching the molecular underpinnings of systems so intricate and complex can be daunting. Even so, Nayak draws inspiration from her patients.

"They are unique in the sense that rheumatologic disease impacts all age groups, and their diseases are chronic," she said. "The diseases are so complex and often just getting to a correct diagnosis is a challenge in and of itself. My patients teach me so much about how differently the same disease can impact each person."

"As a scientist, this is a rich opportunity to tackle a challenging problem that affects a large percentage of the human population," said Nayak. "As a clinician, I also get to know my patients over the course of their lives and participate in their life events—graduations, marriages, children's birthdays, and more."

Nayak's interactions with patients provide a strong motivation and guiding force for the types of questions that she will present in the lab, she said.

"Patients tell me about their struggles, symptoms and side effects, and I recognize this as an opportunity to improve medicine," said Nayak. "To be able to take what my patients are telling me in the clinic and then design and implement studies that help to address these struggles—this is an amazing privilege as a physician-scientist."

"Furthermore, being immersed in research makes me realize how little we know about human and disease biology," she said. I find that bringing this humility back into the clinic is valued by my patients."

Q and A: An Interview with Dr. Rachel Nosheny

Q: How did you become interested in neuroscience?

A: As an undergraduate at the University of Pennsylvania, I was a psychology major, very interested in studying mental illness. Searching for courses, I discovered a major called Biological Basis of Behavior. I had no idea what that meant. I signed up for a class about biological mechanisms of brain disease. This was my introduction to cell biology. The fact that cell biology could help explain such complex human experiences as mood, thought, emotion—that idea was absolutely fascinating to me. That experience put me on a clear path to becoming a neuroscientist.

Q: Your research shifted from the lab to clinical neuroscience, including developing strategies to identify risk of cognitive decline and Alzheimer's disease. Why did you shift?

A: I love cell and molecular biology. I love the methodical, precise way that basic science approaches ask and answer complex research questions. I'm very grateful for everything I learned doing this type of research as a graduate student and postdoctoral fellow. Transitioning out of my postdoctoral work, I had a desire to be more directly connected to individuals affected by the disease. I wanted to be part of the work that really moves the insights from basic science into treatments that help individuals and families. I found that in clinical dementia research.

Q: One of your research mentors is Dr. Michael Weiner, a pioneer in Alzheimer's disease research. How influential has he been?

Rachel Nosheny, PhD

Associate Professor in Residence

Weill Institute for Neurosciences, Department of Psychiatry and Behavioral Sciences

Department of Radiology and Biomedical Imaging

University of California, San Francisco

Associate Professor

VA Advanced Imaging Research Center

San Francisco VA Health Care System

A: Extremely influential. Mike is a visionary leader and a remarkable scientist. I've learned so much from observing the way he thinks, how he tackles challenges, and the way he treats those around him. He is wise, generous, honest, kind, and lots of fun to work with. Working with Mike is never boring! I feel incredibly grateful to have him as a mentor.

Q: You helped start the Brain Health Registry (BHR). Please explain its importance and how it has grown.

A: Recruitment of older adults for Alzheimer's, aging, and other clinical studies is expensive, time consuming and it delays clinical trials and observational studies. Many studies have inadequate recruitment; this affects the pipeline for development and testing of new treatments. It's slowing us down.

The BHR platform addresses this by making clinical research more efficient, less expensive, and accessible to more people. The BHR is a digital, online platform for recruitment, screening, assessment, biomarker collection, and longitudinal monitoring of clinical research participants. All study tasks are completed by participants online, at-home, at their own pace, and on their own device. Our approach makes research highly scalable. We have been enrolling people since 2014 and now have over 106,000 enrolled!

We have used the data we collect to further our understanding of many aspects of brain health, including the many factors that influence memory and thinking. We also have over 75 collaborations with other researchers, enabling them to use our data and online platform to conduct their own studies.

In short, it's been a highly productive and rewarding effort so far, and we think it has the potential to continue to have a huge impact on Alzheimer's disease and other clinical research, clinical trials, and even healthcare strategies.

Q: How are you and BHR increasing diversity in Alzheimer's disease research studies and why is

that crucial?

A: To ensure that research and newly developed treatments work well for everyone, it is crucial to get many different types of people to participate in research and clinical trials. We know that many factors affect people's health and how they might respond to a treatment, from their genetics to their culture to the environment they live in. It's just good science to include everyone.

The Alzheimer's disease field has made progress to address this issue, but we still have a long way to go. BHR has taken a unique approach. We combine digital recruitment (for example, social media advertising) with community engaged research. Community engaged research puts the preferences and priorities of affected communities front and center by forming strong partnerships with community members. This is usually done in-person at a local setting.

We asked, "Can we take the most important aspects of the community engaged approach, and apply them to our highly scalable, digital technologies in BHR?" And we now have several projects demonstrating that approach works.

Q: You initiated the online Caregiver and Study Partner Portal. Please comment on its importance.

A: The Caregiver and Study Partner Portal is an innovative BHR initiative. It allows a participant to join along with their "study partner." The study partner is someone who knows them well and who has frequent contact with them, like a spouse or adult child or grandchild. We now have over 11,000 participant-study partner pairs enrolled.

Why is this important? Involvement of a study partner is required for Alzheimer's disease trials and other studies. Study partners provide unique insight into recent changes in the participant's memory and thinking. Study partners notice changes in ability to perform everyday tasks. These changes are difficult to assess using memory tests alone, yet they are important to families and affect an individual's quality of life.

One crucial role for study partners in dementia research is to step in and accurately report about decline in their loved one's memory and thinking, even once the affected individual loses insight into their own abilities, due to their worsening dementia. For all these reasons, study partners are a very important part of Alzheimer's disease research. Yet there are almost no studies focused on recruiting and engaging study partners. That's the goal of our work in this area.

Q: For someone who started as a lab scientist, you seem very connected and compassionate to study participants, particularly Veterans. Were you always that interested in the "patient" or was it something developed on the job?

A: This was a major motivation for my transition to clinical research, and more specifically, to conducting community engaged research. With all my background in the biology of Alzheimer's disease, I didn't really know anything about the disease until I started working with community members.

It's so motivating to hear firsthand about patient experiences, patient concerns, and what is truly important to individuals and families. Ultimately, that guides my work. It requires a lot of listening and sustained commitment to bi-directional learning: from patients to researchers, and researchers to patients. We have a lot to learn from each other.

Q: What would most people be surprised to know about you?

A: In high school, I dreamt of becoming a poet. Science was not even on my radar. I still write a lot. Nowadays, my poetry habit is channeled into song writing for a rock band I started with my husband.

Interested in participating in the Brain Health Registry?

Help speed up the discovery of treatments with the Brain Health Registry. It starts with just a few minutes of your time.

If you are 18 years or over, you can help the Brain Health Registry speed up the discovery of treatments for Alzheimer's, Parkinson's, depression, PTSD, and other brain disorders. It takes just a few minutes to get started. For most people, participation takes less than three hours per year.

For more information, visit https://www.brainhealthregistry.org/

NCIRE Welcomes New Board Members: Drs. Salomeh Keyhani and Karen Seal

Salomeh Keyhani, MD

Dr. Salomeh Keyhani is a Professor of Medicine at the Univesity of California, San Francisco (UCSF), and Staff Physician and Investigator at the San Francisco VA Health Care System (SFVAHCS). She is also the Director of the Center for Data to Discovery and Delivery Innovation (3DI), a VA-funded Center of Innovation focused on improving health and health care delivery.

Karen Seal, MD, MPH

Dr. Karen Seal is a Professor of Medicine and Psychiatry in Residence at UCSF, and the Service Chief of Integrative Health at SFVAHCS. She serves in leadership roles with the 3DI Center for Innovation and NCIRE's Women Veterans Research Collaborative, through which she is mentoring the next generation of health services researchers.

Learn more about Drs. Keyhani and Seal, and our full Board of Directors: https://www.ncire.org/board-of-directors

PI and Research Highlights

Dr. Alexander K. Smith co-published a Poetic Analysis of End-of-Life Caregiving in the Journal of the American Geriatric Society

NCIRE-supported Principal Investigator, Dr. Alexander K. Smith, co-published "By the Time We Knew...": Poetic Analysis of End-of-Life Caregiving Experiences for Rapidly Progressive and Slower-Duration Dementia Syndromes in the Journal of the American Geriatric Society (JAGS).

This secondary qualitative analysis compares end-of-life experiences for caregivers of decedents with different dementia subtypes. It includes 10 poems whittled from interview transcripts and a new conceptual model of dementia end-of-life experience. The interdisciplinary team includes former MSTAR students, postdocs, GBHI Atlantic Fellows, and faculty colleagues across UCSF and the U.S.

Read more: https://agsjournals.onlinelibrary.wiley.com/doi/10.1111/jgs.19382

External Validation of the Walter Index for Posthospitalization Mortality Prediction in Older Adults

NCIRE Board Member, Dr. Louise C. Walter, and her fellow NCIRE-supported investigators, Drs. John Boscardin, Sei J. Lee, Kenneth E. Covinsky, and Alexander K. Smith join a research team to investigate whether the Walter Index predicts posthospitalization mortality in older adults outside the U.S.

The Walter Index is a widely used prognostic tool for assessing 12-month mortality risk among hospitalized older adults. Developed in the U.S. in 2001, its accuracy in contemporary non-U.S. contexts is unclear. The research team evaluates the external validity of the Walter Index in predicting posthospitalization mortality risk in Brazilian older adult inpatients.

Read more: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2829452

New Federal Funding Awards

Congratulations to the following Principal Investigators for your recently funded awards!

Jialing Liu, PhD
Project Title: Type 2 Diabetes Induced Chronic Inflammation on Stroke Outcome
Sponsor: National Institute of Neurological Disorders and Stroke
Award Received Date: 11/29/2024

Kristine Yaffe, MD
Project Title: Early Mid-life Environmental Toxicant Exposures and AD/ADRD Risk in CARDIA
Sponsor: NIH via subaward from University of Pennsylvania
Award Received: 12/04/2024

Sei Lee, MAS, MD
Project Title: Deprescribing Cardiovascular Medications among Persons with and without Alzheimer's Disease and Related Dementias in Long Term Care
Sponsor: NIH via subaward from Palo Alto Veterans Institute for Research
Award Received: 12/12/2024

Duygu Tosun-Turgut, PhD
Project Title: The Progressive Supranuclear Palsy Clinical Trial Platform (PTP)
Sponsor: NIH via subaward from UCSF
Award Received: 01/06/2025

Maren Scheuner, MD, MPH
Project Title: The VA Genomics Learning Health System: Implementing Genomic Medicine Across Diverse Veteran Communities
Sponsor: NIH via subaward from Boston VA Research Institute
Award Received: 01/22/2025

Raymond Swanson, MD
Project Title: Investigating Novel Genetic Variants that Confer Susceptibility to Pesticide-induced Parkinson's Disease in Human Neurons
Sponsor: NIH via subaward from J. David Gladstone Institutes
Award Received: 02/20/2025

Funding Opportunities

Industry Opportunities

Please contact Newton Ong, newton.ong@ncire.org, or Adan Pinedo, adan.pinedo@ncire.org, for further information on the following Industry Opportunities.

Johnson & Johnson
A Study of Bleximenib, Venetoclax and Azacitidine For Treatment of Participants With Acute Myeloid Leukemia (AML) (cAMeLot-2).

MCRA/IQVIA
Seeking VA sites to test a unique, state of the art and innovative technique to determine the stage and type of cancer from a simple blood draw (liquid biopsy).

Roche Diagnostics
A pilot program collaboration centered around our Navify Clinical Hub product. Navify Clinical Hub is a disease management workflow solution designed for interdisciplinary care teams in the oncology space.

Please visit the Office of Sponsored Research page on the NCIRE SharePoint at https://ncire.sharepoint.com/ or click here for the full list of Industry Opportunities.

Federal Funding Opportunities

Please contact Jessica Schmidt, jessica.schmidt@ncire.org, for further information on the following Federal Funding Opportunities.

NIH: Innovative Mental Health Services Research Not Involving Clinical Trials (R01 Clinical Trials Not Allowed)
(PAR-25-283)
National Institute of Mental Health
• Application Deadlines: June 5, 2025; October 5, 2025

Funding Opportunities continued

NIH: [Grand Opportunity in Medications Development for Substance-Use Disorders (U01 Clinical Trial Optional)] (PAR-25-328)
National Institute on Drug Abuse
• Application Deadlines: April 10, 2025; August 11, 2025

NIH: [Research on Current Topics in Alzheimer's Disease and Its Related Dementias (R21 Clinical Trial Optional)] (PAR-25-331)
National Institute on Aging
• Application Deadlines: June 16, 2025; October 16, 2025

Please visit the Office of Sponsored Research page on the NCIRE SharePoint at https://ncire.sharepoint.com/ or click here for the full list of Federal Funding Opportunities.

In the Helix

Petronela Buiga, PhD, DDS-MBA
NCIRE Research Scholar, Dr. Robert Nissenson Lab

Q: What is one thing, big or small, you did last year that you will never forget?

A: One of the biggest things I did was joining Dr. Robert Nissenson's research team through NCIRE. His team inspires me every day. Everyone at Mission Bay, including my lab colleague, Dr. Vikrant Piprode, is amazing—it truly feels like a family while maintaining an extremely professional environment.

Q: What's your hidden talent?

A: My hidden talent is quickly connecting with people. I've lived, studied, and worked in 5 countries across 3 continents. I've visited 35 countries in total. I've been exposed to many cultures and have come to appreciate that every person is unique and knows something I don't.

Q: What's something you've done from your "bucket list"?

A: I'm actively working my goal of advocating for rare diseases. In February 2025, I participated in Rare Disease Week on Capitol Hill in Washington D.C., where I helped advocate for legislative initiatives by meeting with congressional members. As a scientist, I find it essential to bridge the gap between research and real-world impact.

Keith Chan
NCIRE Information Technology Director

Q: What is one thing, big or small, you did last year that you will never forget?

A: I rode a roller coaster for the first time. I still remember how fast my heart was beating when it climbed up, and I grabbed onto the handle tightly when it started to drop. It was a thrilling experience and unexpectedly fun.

Q: What's your hidden talent?

A: I guess I have a bit of talent in cooking. When my oldest daughter asks me to recreate restuarant meals at home, and I deliver most of the time. Whenever I make a dish for the first time, my family are like the judges in a cooking contest, and I am like a contestant anxiously awaiting their feedback. It is a fun interaction.

Q: What's something you've done from your "bucket list"?

A: Traveling is something I like, and my bucket list is filled with places I would like to visit. So far, I have been to the Grand Canyon, and the view is breathtaking. Hopefully I will be able to scratch another one off my list soon.

If you know an NCIRE employee and would like to be featuered in *In the Helix*, contact us at **dna@ncire.org**.

Message from the Chief Executive Officer

Three months into the calendar year, and 2025 has brought many changes. Change is an opportunity for growth, and it is with this mindset that we continue to navigate through the evolving landscape.

Thank you for the contributions to the Spring 2025 Newsletter from Renuka Nayak, MD, PhD and Rachel Nosheny, PhD, who have shared their respective research. Their time and commitment are invaluable and appreciated.

As a proactive fiscal measure, NCIRE has paused funding for new Recruitment, Momentum, Propel, and Clinical Scientist Pilot Awards. These programs are funded via the Indirect Cost funding pool. While we recognize these programs offer significant value to the research community, we need to carefully balance financial obligations. As circumstances allow, we will reassess and resume these funding opportunities.

The annual financial statement audit and federal program compliance audit was recently completed for Fiscal Year 2024 (10/1/2023-9/30/2024). The audit report indicated an unmodified opinion or a clean report, financial statement presented fairly in all material respects and in accordance with U.S. GAAP. NCIRE continues to demonstrate compliance with Uniform Guidance (2 CFR Part 200): 2 CFR Part 200 establishes uniform administrative requirements, cost principles, and audit requirements for Federal awards to non-Federal entities. Maintaining an unmodified audit report and low risk designation demonstrates to funders and collaborators compliance with all necessary standards. The report can be found here.

Recently, NCIRE has updated the policy on use of NCIRE Indirect Accounts. Animal related-costs (e.g. purchasing of animals; housing) and equipment cost greater than $10,000 per unit are disallowed on Indirect Accounts. The change is driven by the Uniform Guidance and the definition of indirect costs. NCIRE Indirect Accounts include PI Administrative Accounts, Research Support accounts, Recruitment Funds, and the Core Office administration. Please see here for the updated PI Administrative Account policy and here for the updated Recruitment Award Policy.

As of March 7, 2025, there are thirteen (13) new awards for fiscal year 2025, two (2) NIH Prime awards, nine (9) federal subcontracts, and two (2) Industry awards (CRADA). In comparison to the same period last year, there were sixteen (16) new awards; while there is a decline, we remain optimistic. On the application side, there have been sixty-seven (67) new applications year-to-date. When compared to the same period last year, there were thirty-nine (39) applications, a significant increase.

Thank you for taking the time to read the 26th edition of the Spring 2025 Newsletter. Please let me know if you have any questions or comments.

Rebecca Rosales, MBA, CRA
Chief Executive Officer

About NCIRE

NCIRE - The Northern California Institute for Research and Education, Inc. has one mission and one goal: Advancing Veterans Health. We sustain a scientific community of clinicians and researchers and support nearly 200 researchers who have joint faculty appointments at the University of California, San Francisco (UCSF) and the San Francisco VA Health Care System (SFVAHCS) and are working to foster innovation through leadership in the field of Veterans health research. Our broad portfolio of projects receives generous support from the National Institutes of Health, the Department of Defense, and individual donors, making us the largest nonprofit research institute devoted to Veterans health in the US.

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