NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION, INC.

DNA

DETAILS NEWS AWARDS

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Focus on Research

Feeling Veterans' pain, developing solutions

"The pain is all in your head" might be an insensitive remark to an aching person.

Yet there is scientific truth to that comment. While pain is felt in body tissue—after an injury or due to a chronic condition—the brain is the ultimate interpreter and processor of pain signals. Thus, pain is in your head, and it is quite real.

In 2023, 24.3% of U.S. adults experienced chronic pain, according to the CDC. Pain is also more prevalent among Veterans. One NIH study found that 65.6% of Veterans reported having pain in the three months before the survey (compared to 56.4% in the general population), and 9.1% of Veterans suffered severe pain.

How the brain creates the experience of pain is complex. In some people, there is a clear reason for their pain—a burn, a cut or disease such as arthritis. But for others, there are no obvious physical roots, and their chronic pain is caused or exacerbated by psychological trauma. Among Veterans, for example, chronic pain often goes together with conditions such as post-traumatic stress disorder (PTSD), depression, or other anxiety disorders.

Dr. Irina Strigo, an NCIRE-supported scientist at the San Francisco VA Health Care System (SFVAHCS), conducts groundbreaking research that has greatly advanced the understanding of the neurobiological mechanisms of pain perception, particularly in trauma and affective disorders.

Irina Strigo, PhD

Professor-in-Residence of Psychiatry and Behavioral Medicine
University of California, San Francisco

Research Career Scientist
San Francisco VA Health Care System

Principal Investigator
Emotion and Pain (ePain) Laboratory
San Francisco VA Health Care System

Strigo is a Principal Investigator of the Emotion and Pain (ePain) Laboratory, which integrates various disciplines, from physiology to psychology and radiology, to understand the co-occurrence of physical pain and mental health issues. The lab unites techniques such as brain imaging and pain and sensory evaluation to create a picture of the mechanisms behind the pain and

emotions that individuals are experiencing.

"I'm genuinely excited about several promising developments that are beginning to bridge the gap between our neuroscience discoveries and clinical practice," said Strigo. "One of the most powerful insights from our research has been identifying distinct neural phenotypes among Veterans with chronic pain."

"We're finding that despite similar symptoms, there are fundamentally different brain mechanisms at play in different individuals," she said. "This isn't just academically interesting—it has profound implications for treatment."

Her lab's research could lead to individually tailored treatments, including non-opioid interventions. "Our work has identified neurobiologically dissociable biotypes with different mechanisms for managing pain and trauma," said Strigo.

"Understanding these individual differences means we can potentially match patients to the treatments most likely to work for their specific brain profile, rather than the current trial-and-error approach."

A passion for pain research

Strigo's appreciation of the complexity of pain goes back to her undergraduate days at McGill University in Montreal when she was learning about substance P, a neuropeptide that is crucial in transmitting pain signals from the spinal cord to the brain.

"When it came time to do my honors thesis, I knew I wanted to focus on pain physiology, but I was hesitant about the animal work. To be honest, I was scared of rodents," said Strigo. "This led me to seek alternatives, and I was fortunate to come across a human pain fMRI lab. That was really the beginning of my journey in this field."

The concept of emotional pain was difficult for her to grasp at first, but after her PhD studies she shifted from pure pain neuroscience to depression research.

At UC San Diego (UCSD), from 2007 to 2014, Strigo developed a pain program with colleagues who specialized in pure depression, PTSD, and traumatic brain injury (TBI). She conducted studies at the VA San Diego Healthcare System, serving as Chief of the Stress and Pain Unit for the Center of Excellence for Stress and Mental Health (CESAMH). "Working alongside these experts made it clear that pain intersects with so many other conditions—it simply couldn't be studied in isolation," she said.

Collaboration is critical

When Strigo came to UC San Francisco (UCSF) and SFVAHCS in 2014, she built her human pain research program from scratch. "I quickly realized that to address the complex interactions between pain, trauma, brain injury, and mental health conditions, I needed expertise from multiple disciplines. No single perspective could capture the full picture," she said.

"Today, our program collaborates with five programs at SFVAHCS, multiple departments at UCSF and UCSD, and partners at the University of Pittsburgh Medical Center, not to mention our industry connections," she said. "My network now includes over 120 collaborators across eight countries, which reflects just how multifaceted pain research has become."

The ePain Laboratory is really the embodiment of this multidisciplinary approach, she said. "When I established it at SFVAHCS in 2014, I deliberately designed it to be a hub where various disciplines could converge around the complex problem of pain."

"What sets our lab apart is that collaboration isn't something we talk about in meetings—it's how we actually get work done," said Strigo. "We've created an infrastructure that facilitates meaningful partnerships across institutional boundaries. For instance, we've developed robust methods for collecting patient-reported outcomes that continued even during the pandemic, providing critical data to researchers throughout our network."

Groundbreaking research

In the last 15 years, Strigo has conducted and published several landmark studies.

In 2008, she was the first to identify and show differences in interoceptive processing in major depression. She coined the term "emotional allodynia"—a phenomenon where individuals with conditions like major depressive disorder (MDD) experience a heightened negative emotional response to stimuli that are not normally painful.

Strigo was the first to demonstrate alterations in brain response to pain among individuals with PTSD via avoidant mechanisms and in TBI through aberrant endogenous pain modulation. These findings are reshaping pain management strategies for Veterans with those conditions.

In a 2022 study of Veterans using MRI, her lab discovered

three different types of brain patterns that may explain why some people are more prone or less prone to chronic pain. The findings counter the one-size-fits all approaches to treatment and instead point to more tailored treatments for individuals.

Compassion for Veterans

Strigo's work with Veterans over the years fuels her research drive.

"My connection to Veterans' health wasn't something I initially set out to pursue—it evolved organically through my research path and the people I encountered along the way," she said.

"What struck me most was the remarkable resilience I saw in these individuals," said Strigo. "Here were people who had endured extraordinary circumstances and were still fighting—not just for their country, but for their own wellbeing. That courage was inspiring, and it fundamentally shifted my perspective on what it means to confront pain and trauma."

"As I delved deeper into the neurobiological mechanisms underlying their conditions, I became more invested in translating our discoveries into practical interventions that could make a real difference in Veterans' lives," said Strigo. "This wasn't just academic curiosity anymore—it was about addressing an urgent need in a population that had sacrificed so much."

In terms of concrete interventions, Strigo says her lab is making real progress with non-pharmacological approaches. "I'm particularly encouraged by our recently funded study with Dr. Laura Case (UCSD) on weighted blankets for Veterans with co-occurring chronic pain and sleep issues," she said. "It's a simple intervention, but our preliminary data suggests it could make a meaningful difference in quality of life for many Veterans."

Digital health tools are another frontier with enormous potential. "We're collaborating with Dr. Wolf Mehling (UCSF) on the 'Mind Your Pain' mobile app, which provides interoceptive attention training to chronic pain patients. Our early neuroimaging results show promising changes in brain activity associated with using this tool."

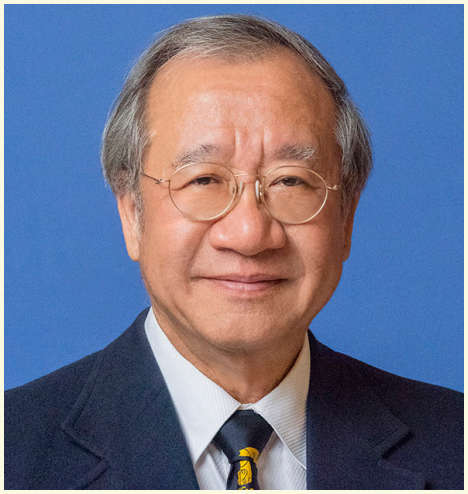
"Looking further ahead, I believe our deep phenotyping approach will transform how we conceptualize and treat pain," she said. "Rather than viewing chronic pain as a monolithic condition, we'll increasingly recognize it as a diverse set of disorders requiring personalized intervention strategies."

"What makes me most optimistic is that we're finally moving beyond the opioid-centric approach that has dominated pain management for too long," said Strigo. "By understanding the complex brain mechanisms underlying pain, we're opening up entirely new avenues for intervention that address the root causes rather than simply masking symptoms."

"For our Veterans who have sacrificed so much, this represents a genuine path toward a better quality of life."

Q and A: An Interview with Dr. Chris Lau

Chris Lau, PhD, is a world authority in the genetics of the male-specific Y chromosome and an expert in molecular genetics and animal modeling of human diseases. He has developed a vigorous research program to investigate the contributions of this male-specific portion of the human genome to gender disparities and sex differences in various diseases and cancers.



Chris Lau, PhD
Professor of Medicine
University of California, San Francisco
Research Career Scientist
San Francisco VA Health Care System

Q: Your research career dates back to the late 1970s. What led you to your current research?

A: I was trained in cytogenetics and cell biology in the Graduate School of Biomedical Sciences at the University of Texas M.D. Anderson Cancer Center in Houston and was successful in my graduate research with a good publication record. To extend my scientific and technical capacity, I wanted to learn more about molecular genetics and DNA cloning techniques in my postdoctoral training. In the '70s, the San Francisco Bay Area was the mecca of genetic engineering with UC San Francisco (UCSF), Stanford, UC Berkeley, and many biotechnology startups.

So, in 1979, when Professor Yuet Wai Kan (a world-renowned pioneer in human molecular genetics) at

UCSF offered me a postdoctoral position, I took it immediately and became proficient in recombinant DNA technology.

I developed a set of versatile DNA cloning vectors, called cosmids, and used them to construct several very comprehensive recombinant DNA libraries of the human genome. After our initial 1983 publication in the *Proceedings of the National Academy of Sciences*, we sent the human cosmid libraries to scientists worldwide.

When I became an independent Principal Investigator and an Associate Investigator of the Howard Hughes Medical Institute at UCSF in 1984, I was interested in identifying an under-investigated area—the Y chromosome.

Q: What attracted your interests in the Y chromosome?

A: From a genetic perspective, the only genetic difference between a male and a female human being is the composition of the sex chromosomes—a male has X and Y chromosomes while a female has two X chromosomes. However, one could recognize that there are significant differences between a male and a female in terms of their looks, physiology and disease susceptibilities, among many biological features.

The Y chromosome is one of the key players in the genetic differences between a male and a female. With the recently acquired recombinant DNA technology, I thought I could clone the DNA and genes from this male-specific chromosome and study their functions and learn how they mediate such differences between the sexes in molecular genetic terms. So, I embarked on a research program on the functions of the human Y chromosome.

The human Y chromosome is one of the smallest chromosomes of the human genome. Nowadays, we know that it has lost about 95% of its original genes and retained only 106 protein-coding genes. Significantly, 62% are repetitive gene families. So, there are about 40 genes/gene families on the human Y chromosome. Only 22 genes/gene families located on the male-specific region are most relevant to sex differences between male and female. Of course, when I started in the late '80s, none of this information was known to the scientific community.

Q: What are the roles of Y chromosome genes in human health and disease?

A: When I started, there were only three major loci attributed to the Y chromosome: male sex determination, sperm production (spermatogenesis), and cancer predisposition. In the presence of the Y chromosome, the embryo develops into a male with testes, which makes sperm to later reproduce. If there were mutations in these sex-determining and sperm-producing genes, reproductive disorders, such as X-Y female and hermaphroditism as well as infertility, will develop. The cancer predisposition locus, called gonadoblastoma on the Y chromosome (GBY) came from observations of these patients of disorders of sex development (DSD), who develop a significantly high frequency, 67%, of a benign germ cell tumor called gonadoblastoma in their dysfunctional gonads. Using various Y-DNA probes, scientists began to investigate changes on the Y chromosomes of these patients for clues. Eventually, the sex-determining gene, SRY, was identified by a group of British scientists in 1990. Our laboratory and another laboratory in Germany independently cloned the GBY gene, TSPY, in the early '90s. There are numerous Y chromosome genes contributing to spermatogenesis, cloned by a few laboratories worldwide around the same time.

So, was the story on the Y chromosome over in the '90s? Definitely not. We know that most of the human genes, when mutated/disrupted might not result in diseases or abnormalities that could be easily observed. Yet, they do contribute to the overall pathogeneses of disease/abnormalities through quantitative means, i.e., in additive manners with mutations/dysfunctions of other genes, resulting in various degrees of male biases in incidence, progression and/or outcomes.

Q: What are some examples of such Y-related diseases?

A: Examples include sex differences in incidence, progression and treatment responses in various neurodegenerative and cardiovascular diseases and cancers, like liver cancer. Of course, sex hormones and their receptors could play some roles. However, the genes on the sex chromosomes, particularly the Y chromosome, could also be contributing genetic factors.

One example that involves the Y chromosome in complex

disease pathology is the genetic phenomenon called mosaic loss of the Y chromosome (mLOY), which recently has received significant attention from the scientific community. It happens when some elderly men lose their Y chromosome in some of their peripheral white blood cells; and they have a higher susceptibility/tendency in developing various cancers and diseases, such as Alzheimer's disease and cardiovascular disease, than those without Y loss. Similarly, some tumor cells in men could lose the Y chromosome, and then develop different pathogenic properties of their cancers. The exact functions of the Y chromosome in the physiology and oncogeneses of these somatic tissues are uncertain. It probably exerts pathogenic actions through a "loss-of-function" mechanism(s).

Another group of studies identified selected genes on the Y chromosome, such as the KM5D, a histone demethylase (an enzyme that modifies the chromatin in the cell). When expressed in high levels, it aggravates the colon cancer in men, but not women without a Y chromosome. Thus, the Y chromosome genes participate in the disease processes through a "gain-of-function" mode in this case. Conceivably, those sex-determining and sperm production genes, as well as the gonadoblastoma gene could also participate in such sex differences/biases, if they are aberrantly expressed in cell types outside the testis.

The above studies support the notion that the genes on the Y chromosome could serve some important functions in quantitative manners in other somatic organs beside testis differentiation and sperm production. Because of its evolutionary degradation, some have argued that the Y chromosome could be extinct in a few million years. However, as we learned more about the human Y chromosome, "The report of my death (Y demise) was an exaggeration" - Mark Twain.

Q: During your illustrious career, what have been your most significant achievements?

A: I have experienced a lot of excitement and success, as well as failures, throughout my career; too many to discuss. I will mention a few achievements I have had throughout the years. Hopefully, some yet to come!

In the 1990s, I served as the U.S. Organizer (Chair) in a consortium of international scientists for a series of International Y Chromosome Workshops to assemble the genetic and physical maps of the human Y chromosome in preparation for the Human Genome Project. I co-authored and published all three meeting reports.

In terms of my own research, my most significant discoveries are:

1) Construction and distribution to the scientific community of various highly comprehensive recombinant human cosmid libraries in the early '80s; and development of a highly efficient strategy/method to clone human genes based on functional selection using a shuttle cosmid vector system I developed. The recombinant DNA molecules can be shuttled between bacterial and mammalian cells (including transgenic mice) relatively easy. In fact, we cloned the human thymidine kinase gene in a couple of weeks of simple experiments as compared to those used by others (existing methodology at that time) spending months and sometimes years with intense experimentation.

2) The elucidation of the gene regulatory mechanisms at the time of sex determination and differentiation in the mouse using advanced genomics strategy.

3) Cloning and characterization of one of the first genes from the human Y chromosome: the gonadoblastoma TSPY gene in early '90s and confirmed its candidacy as the gene for this oncogenic locus on the Y chromosome.

4) The most recent one, identifying the TSPY protein as a cancer-testis antigen, which elicits robust immune responses, killing the positive tumor cells in liver cancer. Therefore, TSPY could be an important candidate for the development of immunotherapy for liver cancer, which affects Veterans five times more than the general U.S. population.

Q: Your current research focuses on the proto-oncogene TSPY. Why is it potentially promising?

A: We have shown that when the sperm stem cell is incapable of entering sperm cell differentiation, TSPY promotes uncontrolled proliferation and hence oncogenesis, leading to gonadoblastoma. However, TSPY is also expressed in various somatic cancers, with the highest (33% positivity in men) in liver cancer. So, it is a cancer-testis antigen, normally expressed in the testis but aberrantly expressed in cancer cells but no other normal tissues. We assume that it would promote cell proliferation and thus oncogenesis. However, there is another side of TSPY that we have not recognized until now. It turns out the TSPY protein is extremely immunogenic, i.e., capable

of eliciting robust immune responses and killing of the positive tumor cells in the host.

Naturally, we will investigate the molecular mechanisms for such TSPY immunogenic actions. We also plan to investigate the suitability of TSPY as therapeutic vaccines in treatment of liver cancer in preclinical mouse models. In fact, some preliminary experiments seem to support such possibilities.

In another approach, we plan to develop a class of special drugs called, antibody-drug conjugates (ADCs), in which a specific TSPY monoclonal antibody is conjugated to a potent drug (usually a cytotoxic drug). In such ADCs, the antibody guides the linked drug to the TSPY antigens on the cell surface and delivers the drug into the tumor cells, thereby specifically killing the TSPY-positive tumor cells.

Importantly, patients positive for TSPY in their liver cancers also harbor TSPY antisera (autoantibodies) in their circulation, which can be easily detected by non-invasive serological means. So, in our treatment scheme, male patients will initially be screened for the presence of TSPY autoantibodies in their circulation. The positive ones could then be treated with the cancer vaccines and/or antibody-drug conjugates to be developed in our current project, which has recently been funded with a Merit-review grant, scheduled to start on July 1, 2025. We are extremely excited and optimistic that some highly specific and effective drugs to treat a subset of TSPY-positive liver cancer patients can be developed from our research in the future.

Q: How has your lab benefited by being at the SFVAHCS?

A: There is ample opportunity for interactions among the SFVAHCS investigators, who collaborate with each other in grant development, submissions and joint projects. The Research Office and NCIRE also provide invaluable administrative and logistic support for grant application, award compliance, fund management, financial reporting and facility improvements. Furthermore, there are significant core facilities on campus, such as the Molecular, FACS, and Morphology Cores, among others, that offer tremendous resources to perform our research.

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

A: I am an avid fan of the 49ers and Warriors. I like to hike the trails around Golden Gate Park and Lands End or walk on the beach on a sunny day. I enjoy listening to music during my walks, mostly oldies from the '70s-'90s. I like to attend live musical performances, like Phantom of the Opera, Sunset Boulevard, and Les Misérables. Whenever I visit London or New York, I attend at least one live musical performance.

Funding Opportunities

Industry Opportunity

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

AstraZeneca
A Phase III, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AZD5148 in the Reduction of Recurrence of Clostridioides Difficile Infection in Individuals 12 Years of Age and Above.

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.

DOD: CDMRP Duchenne Muscular Dystrophy Research Program (DMDRP)

The FY25 DMDRP intends to support research addressing Duchenne Muscular Dystrophy (DMD) pathobiology, diagnosis
- Idea Development Award Pre-Application Due: July 25, 2025
- Clinical/Translational Research Award Pre-Application Due: July 25, 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.

Federal Funding Awards

Congratulations to the following Principal Investigators for your funded awards!

Michael Steinman, MD
Project Title: The U.S. Deprescribing Research Network
Sponsor: National Institute on Aging
Award Received Date: 7/19/2024

Phyllis Tien, MD
Project Title: 1/2 Doxycycline for Emphysema in People Living with HIV: The DEPTH Trial
Sponsor: NIH via subaward from Cornell University
Award Received: 8/20/2024

Michelle Estrella, MD
Project Title: Building a kidney monitoring panel to guide therapy in resistant hypertension
Sponsor: NIH via subaward from University of Toledo
Award Received: 8/27/2024

Alfred Kuo, MD, PhD
Project Title: Unilateral Powered Knee Orthosis for Knee Pain and Instability Intervention with the VA Population
Sponsor: NIH via subaward from University of Toledo
Award Received: 11/21/2024

Kathleen Sarmineto MD, MPH
Project Title: Linking Healthcare Education, Access, and Leadership Opportunities for Underrepresented Students
Sponsor: 10,000 Degrees
Award Received: 5/15/2025

In the Helix

Cat Conti
NCIRE Staff Research Associate IV, Supervisor

Q: What movie can you rewatch over and over again?

A: The movie I can watch over and over again is *Everything, Everywhere, All At Once*. Humorous, poignant, action-packed, and fantastical; it hits a lot of different emotions, especially resonating with Asian Americans like myself. It has a lot of depth, small details, and incredible actors; so I can watch it multiple times and catch something new on the next watch.

Q: What is your favorite Summertime activity?

A: Summer is a joyous time when the sun overtakes San Francisco's Karl the Fog. It's the perfect time for an outdoor picnic with music and loved ones, and relaxation by the beach or an outdoor pool. These are my favorite summertime activities because sunshine, connection with others, and water are all very healing!

Q: What advice would you give your 15-year-old self if you had the chance?

A: My advice would be to pay attention to my negative self-talk and to practice self-kindness. I'd remind myself it's okay to not be perfect. Self-compassion is a lesson that takes time to learn, but it's one of the most important things I wish I'd understood back then.

Jason Nguyen
NCIRE Buyer II/Materials Handler II

Q: What movie can you rewatch over and over again?

A: *Raiders of the Lost Ark*! Other than it being simply one of the best action films ever made, the music and nostalgia hits hard with this one. I grew up with this film alongside the likes of Star Wars, Jurassic Park, and the Disney Renaissance; but I would say *Indiana Jones* is easily the one if I see it on TV at home or on vacation, it stays on.

Q: What is your favorite Summertime activity?

A: Enjoying the world around me. Hiking, relaxing at the beach, BBQing, visiting theme parks, and going alfresco dining!

Q: What advice would you give your 15-year-old self if you had the chance?

A: Chase your dreams hard. Don't let failure stop you, but also give yourself grace. Always stay open to new ideas and people.

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

Department Update

NCIRE joins Sourcewell

NCIRE Procurement has recently joined the Sourcewell group purchasing contract, which offers us aggressively discounted prices for the Staples' office supplies catalog. We have joined in the first year of a three year contract stabilizing pricing over this term. Please explore their catalog through NCIRE's punch out environment in Acumatica. If you have any questions please inquire with NCIRE Procurement at procurement@ncire.org.

Message from the Chief Executive Officer

The sunshine heralds the arrival of summer and all the wonderful benefits it brings. I am looking forward to the warm, long summer evenings.

Many thanks to the outstanding contributors of the Summer 2025 Newsletter: Irina Strigo, PhD and Chris Lau, PhD. We are grateful for their interviews and unwavering dedication and commitment to research at SFVAHCS.

On May 13th, I had the pleasure to attend the VA's Research Week kick-off ceremonial event in Washington, D.C. with Deputy Secretary of Veterans Affairs, Paul R. Lawrence, PhD. This year the VA celebrated the 100th Anniversary of VA Research. The ceremony recognized 6 extraordinary VA Researchers link.

As of June 6th, NCIRE has received 19 New Awards:

- 2 NIH Prime
- 1 DoD
- 9 Federal awards PTE Subcontracts
- 1 non-federal award
- 6 Industry Sponsored Agreements (CRADA)

There have been 95 new grant submissions as of June 6th.

NCIRE's Fiscal 2026 budget call has been sent earlier than in previous years, this was to allow for strategic planning as we continue to experience uncertainty surrounding Federal Funding levels. Please be sure to submit the necessary information by July 10, 2025.

The annual NCIRE Principal Investigator and Research Community 2025 Survey is underway; and the survey will close soon. Every voice is important. If you haven't yet participated, please submit your response now here. The survey responses and comments are anonymous. Once the data is compiled, results will be shared.

NCIRE is proud to support Veterans Research at SFVAHCS. Thank you for reading our Summer 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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Please send comments to dna@ncire.org