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FOCUS on Research

Pioneering Neurovirologist and HIV Expert Examines COVID's Effect on the Brain

In April 2020 – just a few months into the COVID-19 pandemic – Dr. Lynn Pulliam was reading news reports about the lingering complications that COVID infected people were suffering.

Along with coughing, shortness of breath, fatigue and joint pain, there were neurological complaints: loss of smell or taste, dizziness, headache, seizures, tingling sensations, sleeplessness, memory, concentration problems, and altered consciousness.

Pulliam is a pioneering neurovirologist who discovered three decades ago how a then mysterious virus – HIV – damages neural cells, which then wreak havoc in the brain.

Up to 30 percent of people with HIV develop cognitive impairment. Pulliam wondered and worried: Can SARS-CoV-2, the virus that causes COVID-19, infect the brain as well as travel throughout the body, like HIV?

Pulliam, a UCSF Professor of Laboratory Medicine and Medicine, and Chief of Microbiology at SFVAHCS, was determined to find answers. She contacted UCSF researchers, who were beginning to conduct a Long-term Impact of Infection with Novel Coronavirus (LIINC) study of adults recovering from COVID-19.

“In addition to collecting clinical data from COVID-19 patient follow-up visits and interviews, LIINC offers a specimen bank,” said Pulliam. “So, we were able to



Lynn Pulliam Ph.D.
Professor of Laboratory Medicine and Medicine, UCSF;
Chief of Microbiology, SFVAHCS

collect plasma samples to analyze in our lab.”

It was an easy shift – from HIV to the COVID virus -- for her SFVAHCS lab. Her current NIH-funded research focuses on extracellular vesicles (EVs) -- microscopic sacs that shed naturally from most cells. These EVs float through the circulatory system carrying cargoes of proteins and RNA that communicate and interact with other cells.

In HIV-infected people with neurocognitive impairment, Pulliam found EVs that contain neurotoxic proteins are able to penetrate the blood brain barrier. These “neuronal-enriched EVs” contain inflammatory

proteins that are not only implicated in HIV-related neurocognitive impairment, but also Alzheimer's Disease and traumatic brain injury.

In fact, her research aims to identify these proteins as biomarkers for HIV-related neurocognitive impairment. Such biomarkers could lead to early and simple blood tests for HIV-infected people who are at risk for neurocognitive impairment.

While HIV and the COVID viruses are certainly different, the EVs shed by affected cells from the two viruses may have very similar travel routes, cargoes and impacts on neurological systems. Pulliam's lab set out to find out.

Findings in COVID alarming

Last spring, Pulliam's team began to analyze plasma from 24 post-COVID patients in the LIINC study and 12 healthy controlled subjects who were not COVID-infected. Eight of the post-COVID people reported neurological symptoms primarily related to memory and cognition, with one experiencing double vision and another noting hallucination. The other 16 post-COVID patients did not report neurological issues. All people had recovered from their acute illness.

"What we found was alarming," said Pulliam. "All 24 of the people tested who presented with lingering complaints after COVID-19 infection, including 'brain fog' – and not just the eight with neurological symptoms -- had many elevated inflammatory and neurotoxic biomarkers in plasma neuronal-enriched EVs compared to uninfected people."

These findings suggested that the COVID patients without neurological complaints at the time may have unconscious problems with cognition.

She also found, "This was in contrast to neuronal enriched nEVs from HIV-infected individuals or those with Alzheimer's Disease who have fewer and different toxic biomarkers."

Pulliam's study, published March 2021, in the journal *Cells*, offered warning signals in the medical community. SARS-CoV-2 continues to infect millions worldwide, and many of those recovering from COVID-19 may be harboring neurotoxic proteins.

More research is needed, Pulliam said. She hopes to continue to follow the original COVID-19 subjects from the LIINC study and add more subjects to analyze.

"We do not know if the neurodegenerative proteins present in the nEVs (neuronal-enriched EVs) of COVID-19 recovered individuals are transient or long-term. If transient, it may reflect ongoing neuroinflammation and a healthy continued elimination of toxic proteins from neurons and subsequent removal in situ by microglia or by circulating peripheral scavenger cells," wrote Pulliam in the journal article. "Alternatively, if long-term, the condition is worrisome, as it may signal continued neuroinflammation or a possible precursor to neurodegeneration, as the cargo contains inflammatory promoters."

If future studies show that the latter is true, the EVs cargo may offer a biomarker to predict which post-COVID-19 patients are indeed at risk of chronic neurological problems.

Like Pulliam's goal for HIV patients, a blood test for potential neurological problems could serve people with post-COVID infection, too.

International Honors:

- Dr. Lynn Pulliam is internationally recognized for her work on HIV neuroimmunology, biomarkers for HIV neurocognitive impairment, and the effects of HIV and aging.
- In 2019, she received the Pioneer in NeuroVirology Award from the International Society of NeuroVirology (ISNV). Dr. Pulliam was one of the original members of the ISNV and has served as President and Meetings Co-Chair for many years. She was also the recipient of the [2009 Women in Neuroscience Lectureship](#) from ISNV.
- Dr. Pulliam has won several scientific awards on the effects of HIV in the brain, including the Prize in Neurovirology from the Drexel College of Medicine.

VA Research Honor Makes It a 'Career'



*Robert Raffai, Ph.D.
Professor of Surgery, UCSF
Division of Vascular and Endovascular Surgery, Director of the
Atherosclerosis Research Laboratory,
SFVAHCS*

As a laboratory scientist, Dr. Robert Raffai devotes his research to understanding why people with diabetes develop the the severe fatty plaques that build up in arteries and cause atherosclerosis.

It's a particularly urgent health issue among Veterans, who are almost three times more likely to have diabetes than people in the general population. Thus, they are at high risk for accelerated atherosclerosis, other diseases, and disabilities stemming from the restricted blood flow to organs and limbs, and premature death.

Dr. Raffai -- a UCSF Professor of Surgery and Director of the Atherosclerosis Research Laboratory, located at the SFVAHCS -- is also on the cusp of turning microscopic culprits implicated in atherosclerosis into a potential therapy.

His work is so impressive and important, that the national VA is supporting his research. This spring, the VA's Office of Research and Development (ORD) granted Dr. Raffai a coveted Research Career Scientist Award. The honor recognizes critical research contributions made by non-clinician scientists. The award also provides five years of salary support so that Dr. Raffai can expand research to improve Veterans' health and well-being.

"This award means a lot to me," he said. "Beyond its recognition for my service to the mission of the VA, the award assures me that leadership at VA Central Office (VCO) is interested in fostering the growth of my research program."

Getting to the bottom of atherosclerosis

For 15 years, Dr. Raffai's lab has focused on exploring the interplay between metabolism and inflammation in atherosclerosis. His team has uncovered pathways through which the fat-binding and Alzheimer's Disease risk-factor protein, ApoE4, affects inflammation as well as the progression and regression of atherosclerosis.

Dr. Raffai's lab also has found that hyperglycemia -- high blood sugar and a hallmark of diabetes -- increases atherosclerosis by enhancing the inflammatory properties of microvesicles that circulate in the bloodstream. These so-called "exosomes" -- microscopic sacs that shed from most cells -- transport cargoes of proteins and RNA to distant cells, where they can impact cell function and behavior. (See article, "HIV Expert Examines Effect on Brain," about exosomes' role in neurocognitive impairment, in this issue of DNA.)

***The VA's Office of Research
and Development, which
emphasizes translational
research that benefits
Veterans, was certainly
enticed by this promising
work when it awarded the
highly coveted "Career
Scientist Award" to Dr.
Raffai.***

Dr. Raffai's studies of plasma from diabetic Veterans, mouse models of diabetes, and cultured cells exposed to high glucose have identified specific immune cells (macrophages) that produce potentially harmful exosomes, which contribute to cardiovascular disease. They also have revealed that the same family of macrophages can generate an opposite effect and trigger anti-inflammatory exosomes.

Dr. Raffai's team is now detecting, isolating, and engineering these protective exosomes for possible use as therapies and biomarkers for atherosclerosis and other diseases.

"Our work on the study of exosomes has come a long way," he said. "And we are confident that we can produce some that will serve as treatments for numerous types of inflammatory diseases, especially cardiovascular conditions."

A goal for VA Career Scientists is to build collaborations so that other research laboratories – locally, nationally, and internationally – can share resources and findings, and ultimately develop therapies for a wide range of conditions and diseases.

Dr. Raffai is a Principal Investigator (PI) or co-PI of nearly a dozen grants. He collaborates with more than 20 scientists from various disciplines, and not just at UCSF and SFVAHCS, but some as far away as Japan and Switzerland. One of Dr. Raffai's proposed projects, for example, will make use of extracellular vesicles technology and findings from his exosome studies to address COVID-related infection and lung inflammation.

Training a new corps of scientists

Another key role of a VA Career Scientist is teaching and mentoring the next generation of research investigators and clinician scientists. This already has been a successful and enjoyable part of his UCSF and SFVAHCS career. Not only has he taught physiology and metabolism to UCSF medical students, he continues to train and mentor graduate students and post-doctoral fellows.

His first post-baccalaureate trainees in the Atherosclerosis Research Laboratory, Jessica Posada and Andrew Birkeland, are now clinical faculty members with active research programs at Harvard University and UC Davis Medical Center.

“Providing mentorship to trainees has been the recipe for my lab’s success. By fostering their scientific creativity and giving them the independence to pursue their own interests, my mentees are able to contribute novel ideas that take my research program to new heights.”

Several others went on to graduate school and postdoctoral training and are successful researchers at major biotech firms and academic research institutes. Three of his trainees also went on to pharmacy school and now have careers in the pharmaceutical industry.

He also mentors UCSF junior faculty keen on developing research programs on lipoproteins and extracellular vesicles as biomarkers and effectors of cellular signaling.

“Providing mentorship to trainees has been the recipe for my lab’s success,” said Dr. Raffai. “By fostering their scientific creativity and giving them the independence to pursue their own interests, my mentees are able to contribute novel ideas that take my research program to new heights. It is an extremely rewarding experience to nurture the next generation of scientists and healthcare professionals and watch them succeed.”

For more information please see <https://raffailab.ucsf.edu>

Q and A: An Interview with Dr. Mary A. Whooley



Mary Whooley, MD, FACP, FAHA, FACC
Professor of Medicine and Epidemiology &
Biostatistics, UCSF
Director, Center for Health Care Improvement
and Medical Effectiveness, SFVAHCS

Q: Soon after your medical training, your research – rooted in your interest in why psychological stress leads to heart disease – had quick and great impact. Clinicians worldwide were literally saying your name. Please explain.

A: In 1997, our team validated a two-question screening instrument for depression in primary care patients. Answers to two simple yes/no questions, which touched on feelings of hopelessness and lack of interest or pleasure, ruled out depression and identify those who may benefit from further evaluation. “Case-Finding Instruments for Depression: Two Questions are As Good as Many” was the title of our publication in the *Journal of General Internal Medicine*. The two questions were quickly adopted and recommended for routine depression screening by the U.S. Department of Veterans Affairs and the U.K. National Institute for Health and Care Excellence. They were included in the 2009 U.S. Preventive

Services Task Force guidelines for depression screening, translated into many languages, and put into use by numerous health care organizations.

Q: In 2000, you designed and conducted research to determine the link between depression and cardiovascular disease, aptly named the “Heart and Soul Study.” What did you find?

A: This prospective cohort study of 1,024 patients with coronary heart disease demonstrated that adverse cardiovascular outcomes associated with depression were not due to expected biological mechanisms, but rather to poor health behaviors, such as medication non-adherence and physical inactivity. Patients with depression don’t exercise, which makes them feel more depressed. It’s a vicious cycle that leads directly to heart disease. Although treating depression can improve cardiac outcomes among heart patients, improving their health behaviors is a more direct approach!

Q: What surprised you about this study?

A: When we started the study, I had no idea that it would go on for so long and fuel such a variety of research. The study participants have now been followed for over 20 years, and more than 80 percent of survivors remain actively enrolled.

The Heart and Soul Study has also provided biospecimens and clinical data that enabled other investigators to evaluate important questions in cardiovascular outcomes research, producing over 175 publications on varying aspects of cardiovascular disease and mental health. Many of these papers were written by residents, fellows, and other young investigators who developed their careers by using data from this study.

During the course of the study, the prevalence of mental illness was not surprising to me. But the inadequacy of treatments and getting patients into treatment was disturbing.

Q: So, after learning that health behaviors, especially lack of exercise, were largely responsible for adverse cardiovascular outcomes linked to depression, you embarked on a study to improve patient participation in cardiac rehabilitation. What were the results of this research?

A: Exercised-based cardiac rehabilitation (CR) is an evidence-based and cost-effective therapy that reduces secondary events and mortality in heart patients. Unfortunately, it is vastly underutilized in the U.S. with less than 20 percent of eligible patients participating.

We found that the largest barrier to participation in CR was logistical:

patients did not attend CR because it was offered only on weekdays and at medical facilities that were often inconvenient to get to. We ended up implementing a telephone-based cardiac rehabilitation program at the SFVAHCS in 2014.

In 2015, we began a study with 235 Veterans at three VAs, including the SFVAHCS, to compare CR at home or in a clinic after hospitalization. With funding from the Patient-Centered Outcomes Research Institute (PCORI) and the VA Office of Rural Health, we were able to quadruple participation in rehabilitation, and demonstrate that clinical outcomes were similar for participants who went to facility-based programs. After this study was completed, the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), the American Heart Association (AHA) and the American College of Cardiology (ACC) published a joint scientific statement recognizing home-based cardiac rehabilitation as an effective alternative to traditional CR program.

Q: How did the “Heart and Soul” and CR studies influence your shift to implementation science, data science and program evaluation research?

A: While conducting these clinical research projects, I noticed surprising gaps between evidence and treatment. I found that moving research into the clinic could sometimes be frustratingly slow. But I also learned that if you

can capture the right data and get evidence into the right hands you can facilitate the implementation of research findings into practice. My work now focused on using data from electronic health records to accelerate the adoption of evidence-based practices into routine health care.

Q: How are you leading that charge?

A: I direct the Center for Healthcare Improvement & Medical Effectiveness (CHIME), a collaboration hub where SFVAHCS researchers, UCSF faculty and postdoctoral fellows conduct innovative research to improve patient-centered health outcomes. Faculty come from a variety of specialties and leverage data from electronic medical records to transform healthcare. We are committed to disseminating our research to the wider community, including patients, providers and other stakeholders.

I also direct the VA Measurement QUERI (Quality Enhancement Research Initiative), which has an Implementation Training Hub at the SFVAHCS. It provides researchers, clinicians, and program office leaders with the foundation of knowledge necessary to adapt and implement evidence-based interventions to improve the care of veterans while addressing local barriers and needs.

A key goal of both of these programs is to develop a workforce at the intersection between data science

and implementation science by training post-doctoral fellows who will comprise a new generation of health services researchers.

We are also excited to start this July a new training program funded by the National Center for Advancing Translational Science (NCATS), the UCSF Clinical and Translational Science Institute (CTSI), and the Department of Epidemiology and Biostatistics. It is called the Clinical Research Informatics Postdoctoral (CRISP) Fellowship, and it will provide tailored training for clinician investigators who seek to improve healthcare through the science of clinical research informatics. We have recently selected our first cohort of three postdoctoral fellows who will start in July 2021.

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

A: I was rejected from 11 out of 12 medical schools and wait-listed for several months before finally being accepted at the twelfth (Boston University). Fortunately, that turned out to be good training for all the rejection I would have to endure in academic medicine!

For more information on the Heart and Soul Study see:

<https://pubmed.ncbi.nlm.nih.gov/23945449/>

<https://heartandsoulstudy.ucsf.edu/heart-and-soul-study-methods-overview-principal-investigator-mary-whooley-md>

In the Helix



Sean Sandin
Contracts and Grants Specialist III



Emily Lum
Staff Research Associate III



DJ Meisner
HR Representative

Q: What would your superpower be and why?

A: This is a tough one as there are so many fun and amazing superpowers that one could dream up. I'll lend my ear to what history has taught me for this one. If I was blessed with a superpower I would choose the power to heal those in need and in the most unfavorable circumstances. Luckily, I'm fortunate to work with folks that are superheroes doing this type of work!

Q: Have you ever completed anything on your "bucket list"?

A: Ugh, I do not have a bucket list but will consider adding "creating a bucket list" to my to-do list.

Q: What was the country you last visited outside of United States?

A: Living in Seattle we are fairly close to Canada in proximity and attempt to take a boat trip to Victoria, BC every summer. So my answer is... What is Canada.

Q: What would your superpower be and why?

A: If I had a superpower it would be teleportation. Not only would it save me a tremendous amount of time and money, I'd also be able to travel and visit a lot more places. Imagine being able to teleport to another country for a quick lunch or dinner.

Q: Have you ever completed anything on your "bucket list"?

A: One thing I've crossed off my bucket list is traveling through Southeast Asia. I was there for four weeks and visited Thailand, Malaysia, Vietnam, Cambodia, and Taiwan.

Q: What was the country you last visited outside of United States?

A: The last country I visited outside of the United States was Uganda. I lived there for six weeks while working on a malaria transmission project with FIMRC. While there I also went on a safari, roasted my own coffee, hiked, watched bull fighting, and whitewater rafted on the Nile River.

DJ Meisner is NCIRE's newest staff member, having joined the HR Team. NCIRE is very pleased to have him onboard.

Bio and Job Interest:

I am a San Francisco native who graduated with a BA in studio art from SFSU June of last year. My art practice centers around the natural environment, neoliberalism, and how we make sense of the world we find ourselves in. I make photographs and sculptures, taking inspiration from contemporary ecologists like Timothy Morton, Jeff Vandermeer, and Hito Steyerl, as well as artists like Olafur Eliasson, Trevor Paglen, and Sean McFarland. I sought out nonprofit work after the severity of the pandemic made it impossible for me to do work that made me feel like I wasn't making a positive impact. NCIRE stood out to me not only because of its mission, but also its location (I frequently photograph the VA campus for my art practice).

Message from the Chief Executive Officer

It is June, and as we approach Summer, we are delighted to publish our quarterly NCIRE newsletter, DNA. This is our 11th publication, and in this issue, we have contributions from Drs. Pulliam, Raffai and Whooley. We are grateful for their time and the opportunity to highlight their research.

In March, NCIRE circulated an employee survey; we were pleased with the results and feedback, and every comment was read and will be considered. The results were published at the end of April, and there was thirty-eight percent response. The results were positive, and we will strive for improvement. The survey will be conducted again next year, and our goal is to see an increased response.

At the end of 2020, an NCIRE employee Diversity, Equity & Inclusion Advisory Group was established. The group is working on various issues including but not limited to education and awareness, communication, and transparency. If you are interested in joining this dynamic group, please send a note to DEI@ncire.org. Please see the latest issue of their newsletter for June in celebration of [Pride Month](#).

This past week, I attended a National Association for Veterans' Research and Education Foundation (NAVREF) Board Meeting. Being a Board member gives me the opportunity to collaborate with other similar VA Non-Profit Corporations. We discussed increasing clinical trial opportunities and ways to leverage our collective expertise. If you are interested in [clinical trial opportunities](#), please follow the link for more information.

I would like to highlight an NCIRE funding opportunity. [NCIRE Clinical Scientist Pilot Program](#) which was established to facilitate research programs for junior clinicians.

Later this Summer, NCIRE will be transitioning our accounting and purchasing platforms to a new software program, Acumatica. The transition will improve functionality and we are excited about the roll out. We anticipate that this will be rolled out approximately in August 2021. Please look for additional communication as the date draws nearer.

Wishing you an enjoyable summer season.



Rebecca Rosales, MBA, CRA
Chief Executive Officer

About NCIRE

NCIRE - The Northern California Institute for Research and Education has one mission and one goal: Advancing Veterans Health. We sustain a scientific community of clinicians and researchers and support over 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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