NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION

DNA

DETAILS NEWS AWARDS

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FOCUS on Research

Basic Science gets the Picture

Basic scientists have a great combination of qualities:

- *Passion* for research that gets to the core – even the molecular and atomic levels – of the mechanisms that give us life.
- *Patience*. A scientist's work is detailed, sometimes painstaking, with eureka moments few and far between. But they aren't deterred.
- *Perseverance*. In their pursuit of knowledge about the nature and behavior of living systems, they constantly encounter new questions. They strive to answer each one until the puzzle is solved.

Gary Cecchini, PhD
Senior Research Career Scientist, Medical Research Service, Chief of Molecular Biology, San Francisco VA Health Care System

Gary Cecchini – Senior Research Career Scientist within the Medical Research Service, and Chief of Molecular Biology at the San Francisco VA Health Care System (SFVAHCS) – balances these traits, which have ushered his 40-year career as a basic science researcher.

"Ever since I was a little kid, I've been fascinated by how things worked," said Cecchini, who also is a UCSF Research Biochemist.

In the last three decades, the objects of his fascination are a group of proteins that assemble mitochondria - the "power plants" in each human cell. Mitochondria take in nutrients, break them down and create essential energy-rich molecules for the cell.

Cecchini has focused on "Complex II," one of five protein complexes that work in tandem, passing electrons through the chain of complexes and to an oxygen molecule. Along the way, some of the complexes pump protons through the wall of mitochondria, producing a gradient of electrical energy.

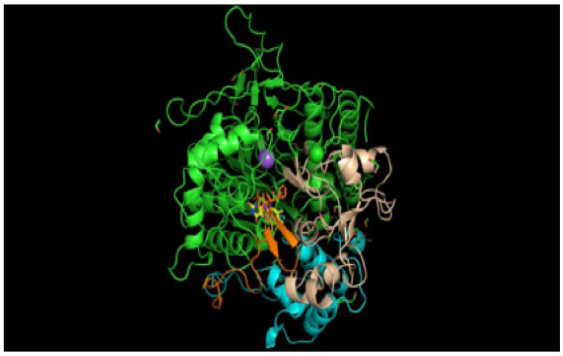
At the end of this chain of complexes, ATP – adenosine triphosphate – is produced. It is the primary energy carrier in all living organisms and central to the health and growth of all life. Without it, cells could not transfer energy from one place to another, making it impossible for organisms to grow and reproduce.

But glitches in the Complex II activity and assembly process disrupt mitochondrial function, said Cecchini. Instead, it delivers damaging oxygen free radicals that

are linked to tumors, heart failure, diabetes, and a wide variety of neurodegenerative diseases such as Alzheimer's and Parkinson's.

Cecchini's task now is to show the architecture of this family of proteins and how they assemble functioning power plants. Knowledge, with every microscopic detail of how these energy-producing plants are constructed will also identify where and how construction and function goes awry.

Researchers like Cecchini can then offer blueprints to other scientists who can develop disease treatments targeted at aberrant activity or misassembled Complex II.



Human Complex II Vitamin B2 containing flavoprotein (green), binding to two human Complex II assembly factors (orange and blue) and the mobile domain of the human flavoprotein (tan).

Landmark discovery

The fact that scientists can now even consider the architecture of these protein complexes is due to breakthrough research done in 1999 by Cecchini, his SFVAHCS and UCSF team members and collaborators at the California Institute of Technology (Caltech).

Although Complex II was first identified about a hundred years ago it is only since the early 1990s that defects within mitochondria have been linked to certain diseases. Cecchini and co-researchers discovered the atomic structure of membrane-bound Complex II in 1999.

The SFVAHCS and UCSF team crystallized the protein, an assiduous process, but one which now allows scientists to view the protein structure under ultra-high magnification. Once crystalized, partners at Caltech imaged its three-dimensional structure via X-ray crystallography. With these images, scientists can use computer modeling to look at arrangements of atoms, ions or molecules and unravel remaining mysteries about Complex II. These images are also well-suited for structure-based drug design.

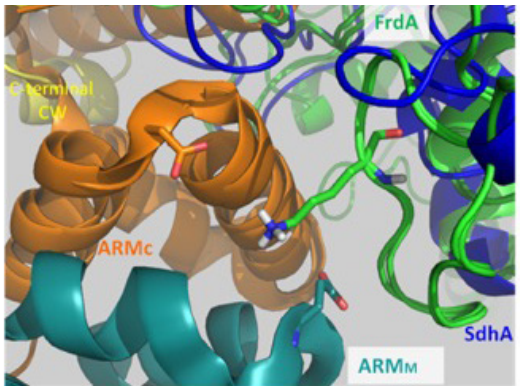
During their landmark research, Cecchini drew on his skills learned in the late 1970s using the recombinant DNA and gene cloning boom. At the time, a significant barrier to studying the structure of membrane proteins like Complex II was the difficulty in obtaining a pure form suitable for crystallization. To obtain enough protein, Cecchini's team turned to the E coli bacterium to genetically engineer an enzyme closely related to Complex II in look and function.

Their work helped give scientists the first picture of Complex II and opened up a new target for exploration and discovery.

Cecchini and other basic scientists around the world employ the knowledge and tools to eventually see and understand fully how these energy-generating complexes do their jobs, or when they fail.

That work is arduous, and the role of basic scientists often is to get thousands of little pictures so that other researchers can pursue the whole picture: potential drugs or treatments for diseases of aging and other ailments.

For Cecchini, being at the SFVAHCS energizes him.



Bacterial complex II (green and blue) binding to the bacterial flagellar motor (orange and cyan)

"As a basic scientist I appreciate working next to clinical scientists because it helps me understand what questions are important to physicians," he said. "I thus can use my expertise to help them formulate questions and find answers to questions that more directly impact patient care."

Gary Cecchini may look at molecular and atom-sized structures, but he also gets the big picture.

Q and A: An Interview with Dr. Michelle Estrella

Michelle Estrella, MD, MHS
UCSF Associate Professor, Medicine
Co-Director of UCSF and SFVAHCS-based Kidney Health Research Collaborative
Chief of Nephrology. SFVAHCS

Q: How did you choose to become a physician and nephrologist? Why did you come to UCSF and SFVAHCS to research kidney disease?

A: I emigrated from the Philippines to Texas when I was 8. I grew up in a family of nurses and spent much of my adolescence in our local hospital – rounding with my dad, shadowing physicians and volunteering as a candy striper. These experiences instilled a sense of service and inspired my interest in medicine.

I became enthralled with nephrology during medical school when I learned of the kidney's intelligent pathophysiology. This interest deepened as I recognized that nephrologists were the physicians who I most admired for their clinical acumen, bedside manner and teaching skills. I also learned firsthand about how devastating kidney disease is for patients and their families.

I increasingly recognized the critical shortage of investigators tackling kidney disease and the urgent need for more research to improve kidney care. Spurred by the excess burden of kidney disease among my patients with HIV, I began my research career focused on reducing this burden. Based on our shared interests, these projects led to long-term collaborations with Dr. Michael Shlipak, who eventually convinced me to make the cross-country move and help build the Kidney Health Research Collaborative (KHRC), which he and Dr. Carmen Peralta established in 2015. Given the KHRC's unique focus on kidney disease prevention, emphasis on mentorship, and team mentality, the move was an easy "sell."

Q: Compared to other fields, why has kidney disease research lagged?

A: First, kidney disease is silent and its impact on a patient's overall morbidity has been underappreciated, taking a backseat to research in cardiovascular disease or diabetes. Second, our field has also been stagnated by the lack of effective diagnostic tests for kidney disease. Our reliance on antiquated tools developed in the mid-1900s can only get our research so far in the 21st century. Third, with some exceptions, our community of scientists and clinicians has generally been complacent, accepting dialysis as the "treatment" for kidney disease. Fourth, there have been under-recognition of the tremendous economic toll that dialysis exerts on the health system, financial incentives to dialysis companies that perpetuate the status quo, and disproportionate lack of innovation in nephrology.

Recent developments, however, give me hope that we're at the cusp of truly addressing the challenges in kidney disease research and clinical care. There is a new spotlight on kidney disease from both the Federal government and private sector. There are amplified voices of patient advocacy groups, and the professional societies have led these coordinated efforts.

Q: What are some of the urgent issues that you and KHRC address?

A: Drs. Shlipak and Peralta were visionary when they emphasized research on the prevention and early detection of kidney disease over a decade ago. KHRC remains true to that vision. We have several projects focused on expanding kidney diagnostics so that they can capture each aspect of kidney health. We believe that these new tools will enable clinicians to identify patients at highest risk for kidney disease, effectively manage conditions like heart failure and high blood pressure, monitor medication safety, and diagnose kidney disease.

Recognizing the significant gap in translating our scientific discoveries to patient care, we've also embarked on health services research to understand the impact of policies on care delivery; identify opportunities to optimize kidney care; and test strategies to improve kidney testing, risk stratification and treatment.

Q: One of your key roles is being a mentor. Why is that important?

A: There are such great challenges ahead for us to alleviate kidney disease that we need all hands on deck. I love sharing my excitement and optimism for nephrology and inspiring interest in nephrology and clinical research through mentorship.

On an individual level, I have the privilege of helping trainees navigate their path through the early career stages; being a sounding board to their ideas, hopes and fears; and serving as a (hopefully) good role model. Mentoring enables me to interact with brilliant young scientists, and their energetic creativity broadens and pushes my own research forward.

Q: Tell us about efforts to improve detection and treatment of kidney disease in Veterans.

A: The CKD Cascade of Care ("C3") Initiative is a multi-stage research program that I lead with Dr. Shlipak. It aims to close the huge gap between the quality of kidney care that we should have and the actual care in the U.S. The ultimate goal is to improve kidney disease detection and treatment for Veterans. The recently funded Phase 1 (VA HSR&D) focuses on making additional laboratory tests for kidney disease available throughout VA facilities and assisting primary care providers to diagnose and treat kidney disease. We are targeting high-risk Veterans who have diabetes, high blood pressure or heart disease. We will also establish the infrastructure and conduct the qualitative work necessary to design and deploy implementation strategies for Phase 2.

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

A: Thanks to my husband, John Clarke, I have developed a near encyclopedic knowledge and collection of single malt scotch.

The Kidney Health Research Collaborative

Four reasons why kidney disease research has lagged:

- **Kidney disease is silent and its impact on a patient's overall morbidity has been underappreciated.**
- **The field has been stagnated by the lack of effective diagnostic tests for kidney disease**
- **The community of scientists and clinicians has generally been complacent, accepting dialysis as the "treatment" for kidney disease.**
- **There has been under-recognition of the tremendous economic toll that dialysis exerts on the health system, financial incentives to dialysis companies that perpetuate the status quo, and disproportionate lack of innovation in nephrology.**

To find out more go to: https://khrc.ucsf.edu/

The Intergovernmental Personnel Act (IPA)

The Intergovernmental Personnel Act (IPA) Mobility Program provides for the temporary assignment of personnel between state and local governments, colleges and universities, and other eligible organizations and the Federal Government. NCIRE is an organization that provides temporary staff to Principal Investigators working on Federal research projects. This mechanism used to facilitate this arrangement is done via an IPA Agreement.

When used appropriately, the IPA is a strategic tool that can aid in furthering research by utilizing skilled and trained personnel on campus. NCIRE provides a service when a Principal Investigator has a VA research project with a "hard-to-fill" research position, where a specific skill set is needed. For example, suppose a Principal Investigator is aware of a qualified NCIRE employee with the skill level required for a particular VA research position. In that case, the Principal Investigator may initiate an IPA agreement to "rent" the NCIRE employee's time on the Federal VA Project. Principal Investigators can begin an IPA by reaching out to the VA Research and Development Office (R & D office). Within the R & D office, there is a team of IPA experts that will explain the forms and provide you with guidance and a timeline to complete the documents.

When completed, the agreement spells out the terms of the contract, confirms funding available, and provides an estimate of work to be performed. The initial contacts can be up to a maximum of two years, and then a new contract can be initiated for an additional two years for a maximum of four years on loan to the SFVAHCS. Once the four-year maximum has been reached, the employee must transfer back to an NCIRE project for a minimum of 12 months before being eligible for another IPA agreement.

To ensure the NCIRE employee qualifies, the below must be true:

- The individual must be employed and charged on an NCIRE project for at least 90 days before an IPA may be executed.
- The NCIRE position being placed on an IPA must be or scientific/research position.
- Administrative staff are not allowed to be placed on an IPA between NCIRE and the VA.
- The Principal Investigator must have NCIRE Administrative dollars to cover the IPA administrative fee of 10% of payroll and benefits each pay period up to a maximum of $5,000 per contract.

To initiate an IPA, the Principal Investigator should:

Contact the Research and Development Office and ask to speak to Beng Dela Fuente at Milagros.Delafuente2@va.gov or contact Eva Lau at Eva.Lau@va.gov.

All Research IPA's must be submitted and approved by the Research and Development Office before routed for other signatures.

Please note that:

The IPA is not approved until all signatures are obtained and the agreement is fully executed.

IPA's may not be backdated. The earliest start date listed may be the date of submission to the R & D office.

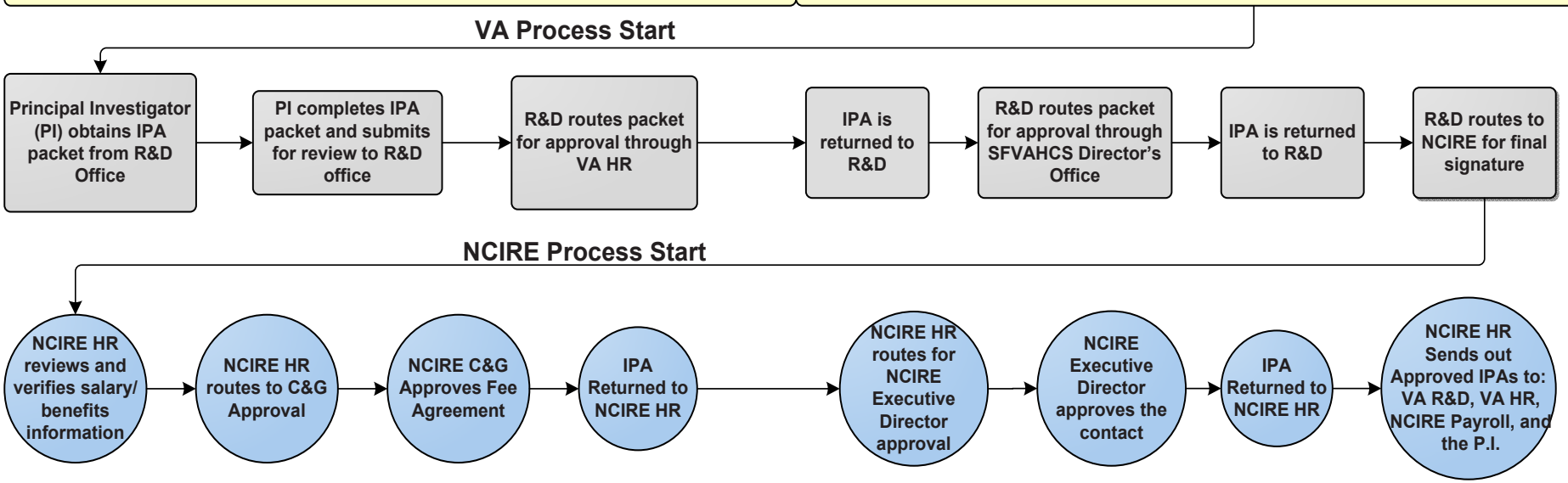
The Intergovernmental Personnel Act (IPA)

What is an IPA?

The Intergovernmental Personnel Mobility Program provides for the temporary assignment of personnel between NCIRE and SFVAHCS. The arrangement occurs via a written contract known as the Intergovernmental Personnel Agreement (IPA). An IPA contract allows a Principal Investigator to rent an NCIRE employee's time for a VA specific research project.

Eligibility

- The individual must be employed with NCIRE and charged on an NCIRE project for at least 90 days prior to an IPA being executed.
- The NCIRE position being placed on an IPA must be a scientific/research position. Administrative personnel are *not* allowed to be placed on an IPA between NCIRE and the VA.
- The Principal Investigator must have NCIRE Administrative dollars to cover the IPA administrative fee of 10% of cost of payroll and benefits, for each pay period, up to a maximum of $5,000 per contract.



IPA Facts

An NCIRE employee may serve on an IPA assignment for up to two years. The assignment may be extended for up to an additional two years, by completing a new contract for the purposes of the extension. After this 2 to 4 year perdiod the employee must return to work on a NCIRE project for a minimum of 12 months.

Renewal IPA Required Documents

1. Funding Availability Checklist
2. OF69 – Assignment Agreement
3. NCIRE Fee Agreement

New IPA Required Documents

1. Funding Availability Checklist
2. OF69 – Assignment Agreement
3. OF306 – Declaration for Federal Employment
4. OF612 or Resume
5. NCIRE Fee Agreement

Message from the Chief Executive Officer

As the Summer of 2020 winds down and we head into the Fall, it is a time for reflection. As the leaves change, I sincerely hope you find moments of happiness and time to do something you enjoy. One of the things I enjoy is recognizing the contributions of our staff that make a positive difference in our lives.

A few weeks ago, Jerry Wong, IT Specialist at NCIRE, noticed an increase in litter on campus. He saw an opportunity to make a positive impact, so he spent a few hours of his weekend back on campus collecting several large bags of litter. This kindness made a big impact. Kathleen/Kitty Stanley, NCIRE Research Nurse, will be retiring at the end of September after 22 years. However, she will not be entirely leaving this work. We are pleased that Kitty will remain on-call to help NCIRE in the future as we work to increase efforts in Clinical and Industry funded research. Having a highly skilled research nurse on-call will be an asset to future research studies.

In July 2020, the US Government Accountability Office (GAO) released a new report entitled, Opportunities Exist to Strengthen Partnerships and Guide Decision-Making with Nonprofits and Academic Affiliates. Congress asked the GAO to review VA's extramural research; specifically, how much was spent on that research in FY2019 and what efforts were made to support medical centers' partnerships for this research. The GAO analyzed policies, documents, and data. It conducted site visits; San Francisco research staff were among those interviewed in October 2019. Also included were officials from VA's Central Office and from a sample of VA medical centers, Non-Profit Corporations such as NCIRE, and academic affiliates. They also selected sites from around the US to represent variation in geographic location and funding. We were glad to participate in the study, since participating in positive change is one of NCIRE's ongoing goals.

As an Affirmative Action Employer, NCIRE annually evaluates our recruitment and employment data, analyzing it for diversity gaps. In fiscal 2019 we noticed a gap in recruiting female managers and supervisors, and we addressed this with new recruitment efforts. I am happy to report that these efforts were fruitful. We will continue focusing on obtaining the most diverse and qualified researchers possible from all backgrounds, regardless of gender, race, ethnicity, and sexual orientation. We are escalating our efforts in 2020 by spending more resources than ever on recruitment efforts that target diversity, disabled individuals, and veterans.

As NCIRE continues focusing on strengthening diversity on our staff, we remain dedicated to the financial health of our employees. NCIREs Retirement Plan is audited annually. We recently completed the report for the period January 2019 – December 2019. The report found no issues with our accounting and that management practices meet and exceed all standards.

Thank you for taking time to read our Fall Newsletter and learn about recent NCIRE activities. Our newsletter is created and edited by a hardworking group of volunteers. We are very interested in your feedback, suggestions or comments. If you are interested in becoming a member of the newsletter committee, please contact me.

Rebecca Rosales, MBA, CRA
Chief Executive Officer

About NCIRE

NCIRE - The Veterans Health Research Institute 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. NCIRE is a 501(c)3 nonprofit. (Tax ID #94-3084159).

Visit NCIRE at **www.ncire.org**

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The Veterans Health Research Institute

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