NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION

DNA

DETAILS NEWS AWARDS

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FOCUS on Research

Research Muscles Up

As an orthopaedic surgeon, Dr. Brian Feeley heals people from all walks of life – young, injured athletes trying to get back on the field, workers hurt on the job, Veterans aching from their time in the military, and older people feeling the wear and tear of aging joints and muscles.

But countless hours in the operating room and clinic aren't enough for Feeley, the scientist. He constantly imagines less invasive and more efficient treatments for patients, faster recoveries, and ways to improve muscle quality after surgery.

So, Feeley, who is Chief of the UCSF Sports Medicine and Shoulder Service, immerses himself in basic research to understand the cellular and molecular changes that occur after injuries. His SFVA laboratory at Mission Bay investigates how stem cells inside the muscle change the tissue and how to stimulate these cells to boost muscle function.

"Being a surgeon, I am able to see what is most important in the eyes of patients, and what the deficiencies are in our basic science knowledge that we need to figure out in order to improve patient outcomes," said Feeley. "This helps focus our research on ideas and studies that are truly translational in nature."

"Being a basic scientist helps me understand the complexities of the human body and acknowledge and respect the little that we actually know about how the body works," he said. "This humility allows me to never accept what we are doing currently as 'the best it is going to get' and always look for new targets to improve patient outcomes."

Brian Feeley, MD
Chief of the Sports Medicine and Shoulder Service,
Professor in Residence at UCSF
Staff Orthopedic Surgeon, Attending Physician, SFVAHCS

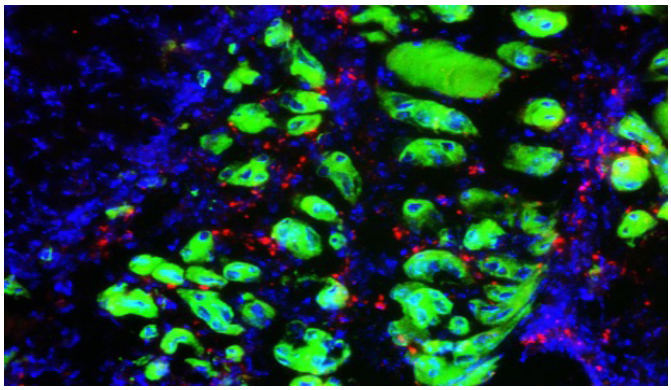
While the laboratory, co-directed with SFVA research scientist Dr. Xuhui Liu, MD, studies muscle tissue and impact on knee and lower back pain, limb immobilization and joint contractures, its key focus is on rotator cuff tears.

"Many people may associate rotator cuff tears with baseball pitchers, quarterbacks and other athletes," said Feeley, who early in his career served as assistant team physician for the New York Giants football team and

currently is the team physician for St. Ignatius College Preparatory High School in San Francisco. But rotator cuff tears are an extremely common cause of shoulder pain and disability in the general population.

"Up to 50 percent of patients over the age of 65 have evidence of a rotator cuff tear," said Feeley.

"Even small asymptomatic cuff tears often progress to larger painful and debilitating tears," he said. And while outcomes of surgical repair of small rotator cuff tears are very good, there has been only limited surgical success for massive tears.



Transplantation of muscle stem cells (FAPs) stimulates rotator cuff muscle to regenerate more quickly with increased muscle quality and better muscle function. (Photo Credit: Feeley-Liu Lab at UCSF).

Fat cells turned good

In his lab, Feeley sees promise in cells that others have long taken for granted. After injury, muscles atrophy as they break down and turn fatty, he explained. Doctors have assumed that these fibrotic and fatty cells formed during atrophy were a result of injury and not helpful to muscle. They also thought all fat cells in muscle were the same and equally useless.

Feeley, however, has found in rotator cuff tissue that certain types of stem cells have high numbers of fibroadipoprogenitors (FAPs), which infiltrate muscle. Over time, FAP cells can turn into white fat, which are energy stores for muscle. They can also become beige fat, which plays an important role in energy balance and secretes growth factors that stimulate muscle regeneration.

"With the right stimulus, these cells can help muscle get healthy again," he said.

Mice as models

After Feeley's lab identified what triggers the changes in the FAP stem cell population after rotator cuff injury, it developed a mouse model that simulates human cuff tears. Researchers in the lab also conduct tiny surgeries that mimic human rotator cuff repair.

Now, they are transplanting into the mice different cells and administering pharmacologic agents to see what happens. At the same time, the lab looks precisely at how beige fat promotes muscle regeneration.

Feeley also uses the same mouse model to study the possible use of specialized microscopic fibers – nanofibers – to deliver stem cells and drugs straight to the damaged muscle and stimulate repair.

His team also began clinical studies with human rotator cuff tear patients to look for and evaluate the activity of FAPs and other stem cells. The results so far suggest that there is an abundant cell source in rotator cuffs that can be put to good use.

"Being a basic scientist helps me understand the complexities of the human body and acknowledge and respect the little that we actually know about how the body works,… humility allows me to never accept what we are doing currently as 'the best it is going to get' and always look for new targets to improve patient outcomes."

"We hope to eventually be able to improve surgical outcomes by influencing the way stem cells in an injured rotator cuff behave after repair," said Feeley. "We'll use the tricks we figured out for stimulating beige fat in mice to prompt humans' own stem cells to help regenerate and improve shoulder function after injury and surgery." His lab is also looking to see whether these FAP stem cells are present in patients with low back pain and spine problems. Finding them in human spinal muscle perhaps could mean a stem source that can be exploited to regenerate muscle similar to what Feeley is doing for rotator cuff muscles.

An aching and aging population is grateful for this research.

Q and A: An Interview with Dr. James Iannuzzi

James C. Iannuzzi, MD, MPH
UCSF Assistant Professor of Surgery,
Division of Vascular and Endovascular Surgery
Staff Surgeon, SFVAHCS

Q: You grew up in Michigan and received your medical education on the East Coast. What brought you to San Francisco?

A: I have had a fascination with San Francisco since high school when my father brought me to a scientific meeting where Craig Venter discussed decoding the human genome. Since then, San Francisco has represented scientific progress, the ideals of inclusion, and a mecca for food and culture. When looking for my first job out of fellowship, I targeted the Bay Area as my top area to reside, but what really got me excited about UCSF and the SFVAHCS was the amazing people here. There are international experts at every turn and a clear commitment to mentorship that underpins the excellence of these institutions. Not only was I plugged in with excellent mentors within the Department of Surgery, including Drs. Julie Ann Sosa, Emily Finlayson and Michael Conte, but was also enamored with the team of geriatricians, including Drs. Louise Walter and Ken Covinksy with whom I immediately clicked with. They have really invigorated me and provided opportunities to make an impact that is just not available at other institutions. There as so many people doing great things here at the SFVAHCS, and certainly my work would not be possible without a large group of excellent clinicians and researchers all focused on improving our approach for vulnerable patients.

Q: As a vascular surgeon, you already have much on your plate, but you also are devoted to clinical outcomes research. Why did you choose this area of research?

A: At an early age I was inspired by my father's work coding the cystic fibrosis gene and have always understood that research and medicine go hand in hand. However, it wasn't until residency that I found my calling for health services research. My path was actually a little serendipitous. I had planned to spend two years in a vascular disease basic science lab, but funding was pulled, and I was left searching for an opportunity. My clinical mentor at the time, Dr. John Monson at the University of Rochester, a visionary colorectal surgeon, stepped in and offered me the chance to be the first in a new clinical outcomes research training paradigm with a focus on advanced training in epidemiology and comparative effectiveness. I felt like I had finally found my research calling and was incredibly excited to apply my clinical knowledge to large datasets and be able to get real data that could help my patients.

Q: Please explain the importance of outcomes research.

A: There is this misconception about medicine that through all the books and knowledge we have gained, we have a good deal of certainty about prognosis and how best to make decisions for any given patient. But the scary reality is that we work in a world with a great deal of uncertainty. In surgery it wasn't really until the investment in and development of large nationally representative quality datasets that we were able to even challenge the many dogmatic assumptions that surgical care has been predicated on. With the advent of large data, we are now able to better predict how any individual will do based on their specific characteristics. This boon in data has allowed us to address the large amount of uncertainty, particularly by applying predictive models and allowing us to provide more personalized care. Just from the start to finish of my surgical training, we have developed new tools that allow any clinician to go online to input the characteristics of the patient sitting in front of them in clinic, and immediately print out their risk for any conceivable outcome for the proposed surgery. This type of real-time risk profiling allows for more informed shared decision-making and informing areas of prior uncertainty. Currently-available models remain rather rudimentary, but in the near future it is likely this type of modelling will be imbedded within the electronic record using real-time data to create

dynamic models that utilize machine learning to help inform our daily decisions.

Q: You have a special interest in the plight of the frail and elderly. How does your research benefit that particular group?

A: You don't have to spend much time in the hospital or even crunching data to realize that older adults, and more specifically those who are frail, disproportionately suffer from more complications, particularly after surgery. As a fellow in vascular surgery at Massachusetts General Hospital, I was struck by how often my patients were surprised that they would need rehabilitation after surgery even in cases where their foot was partially amputated. I realized there were no available prediction models to guide this discussion with patients and worked to create a number of procedure-specific scoring systems to identify patients at high risk for new non-home discharge. However, through this work I realized I was only scraping the surface of the problem and was completely ignoring issues of cognitive impairment, depression and social support, to name a few. My current work has focused on evaluating the impact of depression and cognitive impairment on vascular surgery outcomes. This initial work also highlighted how difficult it is to perform cognitive screening routinely in a surgical clinic, and we are currently working on a qualitative study to help understand and address these barriers. Ultimately, I hope to create a multidisciplinary team focused on optimizing decision-making and preoperative care for older adults faced with vascular surgery. There are many surgical and non-surgical options for patients with vascular disease, and determining the right approach can be complicated and determined by that patient's goals and risk profile. Multidisciplinary care is proven to improve care for cancer patients and is also recommended for older adults being considered for surgery, but practice for vascular patients still lags behind these recommendations. This approach would allow us to incorporate a wider perspective and experience to help our patients make the right decision about surgery, and when surgery is indicated. making sure they are in the best possible condition prior to surgery through nutritional counselling, pre-operative rehabilitation, deprescribing unnecessary medications, and implementing preventive strategies pre-actively to prevent delirium and other preventable complications.

Q: In what other ways are you helping to bolster the outcomes research field?

A: The first step I have taken is to invigorate our trainees to engage in outcomes research. Through mentorship I have been able to help develop a number of residents and medical students that I hope will go on to become leaders in outcomes research in the future. In recognition that there was a need to build a stronger community of health services researchers within the Department of Surgery, I co-founded the Collaborative for Surgical Health, Outcomes, Research, and Equity with Dr. Tasce Bongiovanni. We have worked to provide a venue to discuss ongoing research efforts as well as expose faculty and trainees alike to cutting edge methods and researchers working in this arena.

"You don't have to spend much time in the hospital or even crunching data to realize that older adults, and more specifically those who are frail, disproportionately suffer from more complications, particularly after surgery."

Q: How do you like working at the SFVAHCS and with Veterans?

A: I love it. The unique location of the VA brings an aura to the place as soon as I arrive every day with sweeping views of Ocean Beach and the Golden Gate Bridge. More importantly, the Veterans I work with surprise me on a daily basis and I am often touched by their gratitude and resilience in the face of adversity. They clearly deserve the best possible care and I derive a great deal of pride in treating them.

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

A: I have been enjoying the California lifestyle and recently have gotten into kayaking. Additionally, when I arrived here I joined a band as the lead guitarist and looking forward to getting out there and performing again in the near future.

Pre-Award: Proposal Submission Guide

Submitting a grant can be daunting, but it doesn't need to be. NCIRE's Contracts & Grants Managers and Grants Specialists are here to help. The information here is meant to give an overview of the process so that PIs and their staff have an outline of the steps they will have to take to submit a grant.

Eligibility

Before submitting a grant application, as a prime awardee or a subrecipient, Principal Investigators (PIs) must obtain San Francisco VA Health Care System (SFVAHCS) PI status. To obtain PI status, please contact SFVAHCS R&D Office.

NCIRE uses the online system Cayuse (https://ncire.cayuse424.com), a system-to-system (S2S) solution, to prepare and submit applications to Grants.gov. If you are a new user, please contact your NCIRE Grants Specialist for a Cayuse login and password. If you are unsure of who your Grants Specialist is, please send an email to cgawards@ncire.org and we will assign one to you.

To submit to other funding agencies that do not use Grants.gov, please work with your Grants Specialist. In some cases, separate agency specific registrations are required. Note, registration may take time, so please allow for additional time in your planning process.

Initiating Grant Applications

PIs submitting grants through NCIRE must notify their Grants Specialist at their earliest convenience of their intent to submit and provide a copy of the funding opportunity. This is essential as each funding agency has unique guidelines and we need enough time to review each agency's specific requirements. Completed grant applications are due to NCIRE Contracts & Grants Office at least two weeks prior to submission deadline.

Proposals funded by private industry should be submitted through NCIRE's Clinical Research Center Office. Please contact NCIRE's Compliance & Contracts Manager: cgawards@ncire.org for more details.

Submitting applications to NCIRE for review and approval

All applications must be reviewed and approved by the Contracts & Grants Office prior to submission. PIs must submit application components to their Grants Specialist in accordance with the established timeline.

Application Review/Submission Timeline	
4 Weeks Before Sponsor Deadline	NCIRE applications with subcontracts: complete subcontract package(s) from each subsite are due. Subcontract budgets and justification need to be reviewed, approved, and finalized by NCIRE prior to finalizing prime budget.
2 Weeks Before Sponsor Deadline	Initial review excluding research plan. Final budget, justification, and/or other required documents are due to the Contracts & Grants Office.
1 Week Before Sponsor Deadline	Second review excluding research plan.
3 Business Days Before Sponsor Deadline	Final research plan due.

If the timeline cannot be met, the Grants Specialist will make every effort to submit the application but cannot guarantee a sponsor or NCIRE compliant application; or an on-time submission. NCIRE's Contracts & Grants Office is the sole authority for contacting the awarding agency regarding the negotiation and acceptance of awards. PIs and their staff are asked to contact their Grants Specialist to direct their concerns regarding negotiations of their grants or contracts. NCIRE will contact the awarding agency and keep the PI advised.

All NCIRE administered projects including individual grants, subaward agreements, and contracts require ACOS approval by the R&D committee BEFORE any research may begin.

Eligibility:
Prior to submitting a grant application (as a prime awardee or a subrecipient), Principal Investigators (PI) must obtain San Francisco VA Health Care System (SFVAHCS) PI status. To obtain PI status, please contact SFVAHCS R&D Office

NCIRE's role:
NCIRE Contracts & Grants Office assists VA PIs with submission of non-VA grants (i.e. NIH, DoD, Foundations).

If you do not have a Grants Specialist assigned to you, please contact cgawards@ncire.org

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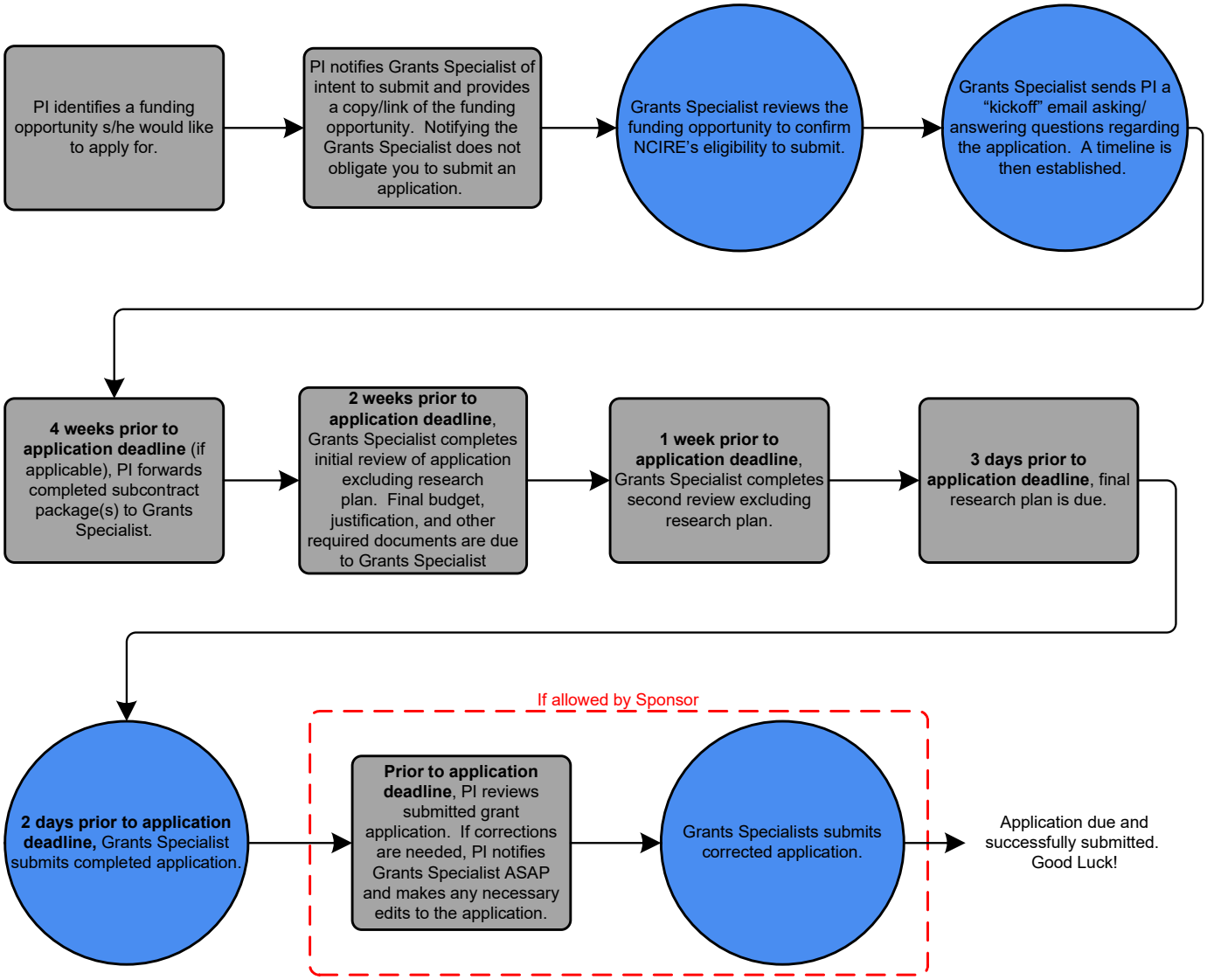

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Legend

PI / Analyst

NCIRE

The Race for a Vaccine

On November 19, 2020, Phyllis Tien, MD, an NCIRE supported PI, and her study team at the San Francisco VA Health Care System (SFVAHCS) successfully enrolled their first study subject into the single-dose COVID-19 Vaccine Study entitled: A Study of Ad26.COV2.S for the prevention of SARS-COoV-2-Mediated COVID-19 in Adult Participants (ENSEMBLE) developed by Janssen: Pharmaceutical Companies of Johnson and Johnson. The SFVAHCS is one of 17 VA sites nationwide participating in the Janssen Trial.

Dr. Tien and her study team are seeking 400 Veterans and non-Veteran health care workers - men and non-pregnant women over the age of 40 years old - to participate in the study, which is expected to enroll participants over a six-week time period from November through the end of the year at the San Francisco VA Medical Center. Those wanting to participate in the study may volunteer by submitting their names at www.va.gov/coronavirus-research.

In the Helix

Bing Sun, MD, PhD
SFVAHCS Medical Center

Q: What's your hidden talent?

A: I like music but I'm not a musician. I like to cook, but I am not a great chef. I like to code, but I am not a computer scientist. I like so much things, I am myself.

Erica Day
Operations and Finance Manager for the Kidney Health Research Collaborative

Q: When you're not working, how do you like to spend your time?

A: I have two young kids (5 years old and 22 months) who keep me pretty busy when I am not working. We love going on family walks, picnicking at parks, and hanging out with friends. When I do get my rare ME time you can usually find me going on a run outside or browsing cookbooks or cooking blogs trying to find the next great recipe to try. I love cooking and baking for my family and friends so that tends to bring me the most joy.

Jerry Wong
IT Support Specialist, NCIRE

Q: If you could instantly become an expert in something, what would it be?

A: Understanding women… specifically my wife. After being married for 20+ years and knowing her for over 30 and getting a degree in psychology…. still a mystery to me.

Message from the Chief Executive Officer

We are approaching the end of 2020, a year we will always remember. Because our rhythms and routines have been so upended, at times it may feel like time is moving quickly and at other times very slowly. I am immensely thankful for the superb teamwork of all at the SFVAHCS campus, everyone is doing their best every day.
It is hard to believe that this is our ninth edition of the newsletter, every article and contribution is thoughtfully considered, and the results are amazing each time.

One of the highlights in our year is that NCIRE has recently established a relationship with Greenphire, a technology company, to provide ClinCards for subject payments. ClinCards are debit cards that can be loaded electronically as needed, and which work exactly like a debit card. This change will increase efficiency for NCIRE, PIs and their teams, and improve the subject experience. If you have an existing study and are interested in transitioning your process to include ClinCards, please contact your Grants Specialist to discuss it.

A new NCIRE Diversity and Equity Council has been established, and our first meeting was December 9, 2020. The Council will be meeting throughout the new year and is looking for members who are interested in participating. Please contact ncirehr@ncire.org to let us know of your interest.

I would like to share grant highlights of the Fiscal Year 2020:

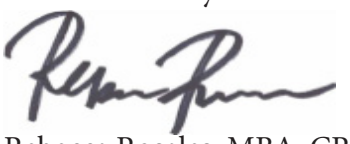
129 total proposals
- 77 Prime applications to federal sponsors
- 46 Subcontracts for federal awards
- 6 Foundation projects

38 New Awards
- 14 NIH
- 5 DoD
- 19 subcontracts on federal awards

14 New CRADA's (industry awards)

These grants represent hours of hard work, investigation, and administration. We are very glad to have supported those of you who have worked to make these grants successful. Successfully supporting our researchers with the highest quality service is our ongoing goal.

Thank you for taking time to read our Winter 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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