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Focus on Research

Medical Imaging Informatics and Artificial Intelligence guide hunt for brain disorders biomarkers

Neurodegenerative diseases, such as Alzheimer's, continue to baffle scientists. But big data analytics and Artificial Intelligence (AI) may offer a clearer picture of what happens in the brains of those who develop and suffer from complicated neurodegenerative disorders.

In Alzheimer's, for example, it is well known that its disease pathology consists of amyloid plaques and neurofibrillary tangles. But not fully understood–nor detectable visually–are the interplay between these two culprits and the complex changes in the brain that cause cognitive and clinical decline.

NCIRE-supported scientist Duygu Tosun-Turgut, PhD, Professor of Radiology at the University of California, San Francisco (UCSF) and founding Director of Medical Imaging Informatics and Artificial Intelligence at the San Francisco VA Health Care System (SFVAHCS), leads a team of neuroscientists, biomedical engineers, computer scientists and biostatisticians that is piecing together "pictures" of the complex brain changes and patterns that cause neurodegeneration.

"The ultimate aspiration of medical imaging informatics and AI in neurodegenerative diseases is to grant clinicians the power to glimpse into the future of their patient's health, intercepting diseases at their most vulnerable stage, and rewriting the story of diagnosis and treatment," said Tosun-Turgut.

"Picture it as a finely tuned telescope, allowing clinicians to peer deep into the brain's complexities. This telescope isn't just about magnification; it's about

Duygu Tosun-Turgut, PhD

*Professor in Residence, Department of Radiology and Biomedical Imaging
University of California, San Francisco*

*Director of Medical Imaging Informatics and Artificial Intelligence
San Francisco VA Health Care System*

the ability to foresee the subtle shifts, like distant stars hinting at future events, aiding in predicting and preventing neurodegenerative conditions," she said.

Tosun-Turgut's research goal is to identify novel biomarkers–early biological signs of disease–that can predict the various stages of neurodegeneration and offer targets for precise treatments.

Her team culls data from thousands of neuroimages, brain autopsies, laboratory specimens, patients' clinical tests, and more, to create algorithms that point scientists to distinctive biomarkers. While computers and machines get the "gee whiz" glamour, the real masterminds behind medical imaging informatics and AI are innovative principal investigators such as Tosun-Turgut, who is also Co-Director of the Center for Imaging and Neurodegenerative Diseases (CIND) at the SFVAHCS.

Pioneering work

"She has been a pioneer in developing tools for multimodality imaging," said Michael Weiner, MD, UCSF Professor of Radiology and Biomedical Imaging and Founding Director of CIND.

"Using advanced bioengineering imaging processing and statistical methods, she innovated methods to bring together structural and molecular information from a variety of MRI and PET images into a common framework and then apply these methods towards answering important questions concerning the pathophysiology of Alzheimer's disease and other disorders," said Weiner, an internationally recognized Alzheimer's researcher who mentored Tosun-Turgut after she joined UCSF and CIND in 2011.

Tosun-Turgut, who has a master's in mathematics and master's and PhD degrees in electrical and computer engineering from Johns Hopkins University, possesses the academic brilliance to be at the forefront of high technology research. Yet it has been her years of work with SFVAHCS and UCSF researchers–and sufferers of dementia of neurodegenerative conditions who participate in studies–that have allowed her to ask the right research questions to bridge data science and clinical investigation.

While many Alzheimer's studies have relied on data from brain autopsies and images and laboratory specimens–such as blood and cerebrospinal fluid– from patients with diagnosed dementia, Tosun-Turgut, in her hunt for novel biomarkers, emphasizes the incorporation of comprehensive data from the living who are at various at stages of diagnoses or potential cognitive decline as they age. Even data from healthy or asymptomatic people add to the critical pool of information.

Researchers have come to agree that neurodegenerative diseases, such as Alzheimer's, are not "one-size fits-all," and that current drugs are ineffective because of the heterogeneity of the disease. As we age, each person has a unique mix of brain patterns–brain cell loss, changes in blood vessels, buildup of abnormal proteins–that

occur over the years, even before symptoms appear. Adding these data points for the algorithms–whether that be from neuroimages, lab specimens, cognitive tests, and more–will better point the way to predictive models of neurodegenerative disease.

Tosun-Turgut also aims to develop and validate biomarkers of neurodegeneration for early diagnosis, to prevent pathologies before they cause irreversible damage to the brain, and to guide clinical studies of therapies.

Recent research

In a study which she will present at an Alzheimer's and Parkinson's disease conference in Lisbon spring 2024, Tosun-Turgut evaluated a protein (α-synunclein) in cerebrospinal fluid as a potential and reliable biomarker that "expands the toolkit for characterizing the heterogeneity across neurodegenerative diseases," she said.

The findings "underscore the importance of considering co-pathologies in dementia research, clinical practice, and future clinical trial design," she said.

In the past two years, Tosun-Turgut has published several studies supporting the inclusion of additional data from a broader base of people at risk of Alzheimer's into studies of the disease and her studies advocate a "precision medicine" approach to clinical trials for "sporadic" and the more common type of Alzheimer's, which is due to a complex combination of factors, including genetics, environment, and lifestyle.

"A trial that includes only participants with pure Alzheimer's disease neuropathological changes (ADNC) would not accurately reflect the general population and could limit the scope of the approved target population unless broader eligibility criteria are evaluated in subsequent trials or eventual clinical practice," she wrote in an article published in the May 2023 issue of *Alzheimer's & Dementia*, The Journal of the Alzheimer's Association. "Therefore, tools for efficient phenotyping to identify both ADNC and non-ADNC will be crucial to measure the effectiveness of these treatments accurately."

Tosun-Turgut advocates for health care equity and access, and for increasing the diversity of patients in clinical trials which helps drive her research.

"The beauty of Artificial Intelligence lies in its transformative potential, reshaping the medical landscape to ensure that precision medicine is not a luxury but a universal right, reaching and benefiting diverse communities by addressing their unique healthcare needs," she said.

Q and A: An Interview with Dr. Alison Rustagi

Q: Please tell us about your research.

A: I'm interested in preventive health care–stopping a problem before it becomes a problem. This is why I went into primary care; and this is what motivates my research.

More specifically, my focus is on lung cancer screening in that it is challenging that we take a healthy person and look for disease. By definition, screening is only done for asymptomatic people. It is hard to make a healthy person feel any better, therefore we have a high threshold to recommend screening.

One tricky aspect of cancer screening is that more information is not always better. There is no benefit from early detection of cancer in a person who will pass away from something else before the cancer would have caused symptoms. This is known as overdiagnosis; and it is a known harm of all cancer screening tests, to some degree. For lung cancer, often the people who are at the highest risk of lung cancer also have other smoking-related illnesses that make the balance of benefit and harm tricky.

We need to be thoughtful with lung cancer screening to ensure we do right by the patient, not over- or under-screening. My goal is to figure out a way to pinpoint who is most likely to benefit and least likely to be harmed by lung cancer screening.

Q: Here at the San Francisco VA Health Care System (SFVAHCS), you are conducting some very important studies on screening for lung cancer (a disease for which Veterans have high incidence/risk). How did you become interested in

Alison Rustagi, MD, PhD

Assistant Professor,
Department of Medicine
University of California, San Francisco

Staff Physician, Division of General Internal Medicine, Medical Service San Francisco VA Health Care System

that specific topic and this study population?

A: I was in graduate school when the first trial was published demonstrating that screening could prevent death from lung cancer. My thesis advisor asked me to lead the departmental journal club on that trial; and I realized how challenging it would be to conduct lung cancer screening in the "real world." That challenge appealed to me. Also, on a personal level, two of my grandparents were Veterans; and working on a disease that disproportionately affects Veterans is gratifying.

Q: Your focus is on "precision prevention." Please explain what that is.

A: Precision prevention borrows ideas that first came out of oncology, in which targeted therapies have been designed that are effective against unique features of cancer cells. Instead of tailoring disease management to a unique type of cancer cell, precision prevention tailors preventive health interventions like screening unique characteristics of a patient. For example, breast cancer screening is different for people who carry worrisome versions of BRCA genes. I want to apply these lenses to lung cancer screening to provide evidence that will allow tailored screening recommendations to maximize the benefit and minimize harm.

Q: How does your clinical experience influence your research?

A: There are so many unique patient situations; and it's a struggle as a physician to feel like there isn't enough evidence to help guide patients' decisions. My goal is to provide the evidence, so primary care physicians and patients can feel like they have solid footing to stand on when making decisions. Sometimes, it is just as useful to know when to screen as it is to know when not to screen and how to talk about that with patients.

Q: What are your key findings so far?

A: We have a long way to go. Overall, lung cancer screening is used far less often than other cancer screening tests.

I have found that more often than not, health professionals will use lung cancer screening once a patient's health is declining. However, this is not ideal, as it is a better practice to screen for lung cancer in an otherwise healthy patient who has a better chance of living to see an averted lung cancer death.

Q: Your research also discovered racial and ethnic disparities in lung cancer screening. How can these disparities be corrected?

A: Yes, troublingly, I found that Black individuals in the general population and in the VA are much less likely to be screened than White individuals, which needs to be rapidly addressed.

White Veterans are three times more likely to be screened for lung cancer as Black Veterans. It's too soon for me to say what needs to be done to address this problem, but it is clear we need to devote time and resources to it. Perhaps most importantly, we need to engage minoritized communities in research and implementation of lung cancer screening; so we can design equitable programs.

Q: What is your goal as you dig further into this research?

A: My overall goal is to bring a simple tool–maybe as simple as two questions–to the clinic to identify people likely/unlikely to benefit from asymptomatic lung cancer detection.

Q: How do you sort so much data and information to eventually offer the needed guidance to clinicians on the critical issues of lung cancer screening and prevention of advanced disease?

A: I receive feedback on my research ideas from a great number of colleagues to see what "sticks" and what needs to be modified to generate clinically useful results.

We're very fortunate here at the SFVAHCS to have such an engaged, supportive group of researchers across disciplines and multiple forums to present works in progress. I feel so lucky to be part of this community and to have benefitted from research mentors at so many points along the way during my time here.

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

A: I'm the third generation in my family to be a VA physician-scientist. My grandfather, Stephen Silvis, was a Veteran and Gastroenterologist at the Minneapolis VA; and his daughter (my aunt), Molly Shores, retired as a Psychiatrist at the VA Puget Sound in Seattle. It's no exaggeration to say that my family members have inspired me.

In the Helix

Jacqueline Holstein
NCIRE Clinical Research Supervisor

Q: What book or film has changed your life the most?

A: *The Fantastic Flying Journey* by Gerald Durrell is a book that has change my life the most. It is a beautifully illustrated children's book that inspired my love for travel and art as a kid.

Q: What crazy activities do you dream of trying someday?

A: One day I would like to hike the Tour du Mont Blanc or become an astronaut and travel to space, but I think the first one is more likely.

Q: Where would you time-travel, if it were possible?

A: If I could time-travel, I would travel to the Mesozoic Era and see the dinosaurs.

May Ng
NCIRE Recruiting Coordinator

Q: What book or film has changed your life the most?

A: The book that changed my life the most is *When Breath Becomes Air* by Dr. Paul Kalanithi.

Q: What crazy activities do you dream of trying someday?

A: I would like to backpack or play tag across Europe. I recently watched a series on the latter; it looked fun!

Q: Where would you time-travel, if it were possible?

A: If time-travel were possible, I would travel 25 years into the future.

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

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Department Updates

Human Resources News - Benefits

NCIRE strives to provide our employees with a generous and robust health insurance package. Taking care of our employees in this way is a key value in our organization's ethos. We strive to have employees who are happy and know they are appreciated.

Although inflation has finally slowed, healthcare prices have not followed suit; the opposite is true. Healthcare costs have increased exponentially over the past 12 months.   Part of this is due to the multiyear nature of typical medical provider contracts that could not pass on increases during a contract period.

Over the years, and as often as possible, NCIRE has absorbed increases to our benefit plans without cost-sharing the increase to our employees. We strive to keep your health care as affordable as possible for you and your family. However, this year, NCIRE has had to average out the past year's increases to specific plans to balance the fairness to all employees.

Our overall rate increase, inclusive of all NCIRE's benefits, was 9.7%. NCIRE continues to absorb a majority of all premium increases. NCIRE continues to pay roughly 84%-85% of premiums for plans offered.

In some plans, specifically the CIGNA Medical participants, employees did see an increase in their monthly premiums by as much as 16%, but that was due to NCIRE having kept CIGNA premiums artificially low for many years by supplementing the plans as a way to offer more choice to our employees. To keep our benefit offering fair and balanced, CIGNA medical participants had to pay a more reasonable share of their plan cost increase than in previous years.

Overall, based on our market data survey collected by a third party engaged by NCIRE, we have confirmed that NCIRE's benefit offerings are generous, competitive, and sometimes exceed the market. Our CIGNA HRA plan is one way we surpass the market by providing a generous HRA contribution and an extremely low monthly premium. We strive to ensure your satisfaction with our benefits offerings and hope you utilize them to optimize your health and well-being.   Please get in touch with Human Resources at ncirehr@ncire.org with any questions or concerns.

NCIRE Office of Sponsored Research (OSR) Update

Beginning January 2, 2024, NIH will require that foreign subrecipients provide the primary recipient access to copies of all lab notebooks, data and documentation that supports the research outcomes described in the progress report. Access, which can be electronic, must be provided at least once per year in alignment with the timing requirements for Research Performance Progress Reports (RPPR). The access requirement applies to all foreign subawards, both new and active. (Reference: NIH Notice NOT-OD-23-182)

NCIRE PIs are responsible for ensuring access and maintaining access for 3 years after the final financial report is submitted. Starting in 2024, OSR will ask PIs to submit an attestation form confirming access to the foreign subrecipient research data along with the annual research progress report. To support the impacted investigators, the OSR team is available to answer any questions; and we encourage you to discuss with your Grants Specialist or reach out to cgawards@ncire.org.

Additionally, OSR will be providing budget projections for all federal sponsored awards on a quarterly basis. FY24 Quarter 1 is expected to close late-January. Grants Specialist will then review and update budget projections and send projections out by mid-February. PIs are encouraged to review and discuss budget projections with their Grants Specialist.

Department Updates continued

IMPROVE Study Keeps on Improving with Dr. Jeffrey Zimmet and His Research Team

In his first ever clinical trial with the IMPact on Revascularization Outcomes of intraVascular ultrasound guided treatment of complex lesions and Economic impact (IMPROVE) study, NCIRE-supported Principal Investigator Dr. Jeffrey Zimmet and his research team were able to secure a Cardiovascular Research Technologies (CRT) 2024 Scholarship for a Principal Investigator, a Sub-I, and SC to attend CRT24 in Washington DC.

The San Francisco VA Health System's (SFVAHCS) IMPROVE study site, was one of only 8 sites out of the 39 site participants to garner the honor.

To secure the scholarship, IMPORVE Study sites had to randomize an average of ≥2 subjects per month, or at least 15 subjects from July 1, 2023 to January 31, 2024. As of November, the SFVAHCS site randomized 30 subjects. Dr. Zimmet's site contributed to the 830 subjects randomized between July and November by the various study sites.

CRT24, the annual CRT meeting, features educational and training sessions that discuss new trial data, explore evidence-based research, and demonstrate the most up-to-date techniques that can be directly applied to clinical and academic practices. It consists of concurrent meetings in six main areas of interest— Coronary, Valve and Structural, Endovascular, Technology and Innovation, Atherosclerosis and Research, and Nurses and Technologists.

Congratulations to Dr. Zimmet and his research team for this fine accomplishment!

Hoops for Troops! NCIRE joins The Golden State Warriors in Celebrating Veterans on Veterans Day

In a remarkable display of camaraderie, 76 NCIRE employees, Principal Investigators, and their families recently gathered for an unforgettable evening at the annual Golden State Warriors Hoops for Troops game against the Cleveland Cavaliers. The air was electric as the NCIRE team enjoyed the thrilling match, creating lasting memories and fostering a strong sense of community. A special thank you goes out to the Warriors for the unique opportunity to witness their warm-up courtside, adding an extra touch of excitement to an already fantastic night. Here's to more shared experiences and team spirit!

From left: Elaine Staats, MPH, CEO of the Palo Alto Institute for Research (PAVIR) and Rebecca Rosales, MBA, CRA, CEO of NCIRE; Golden State Warrior Stephen Curry; Message on the Chase Center Jumbotron welcoming NCIRE and guests to the Hoops for Troops event.

Funding Opportunities

Industry Opportunities

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

Henlius Biotech
A Study to Evaluate the Efficacy and Safety of Serplulimab + Chemotherapy
(Carboplatin - Etoposide) in Patients with Extensive Stage Non-Small Cell Lung Cancer
11/15/23

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

Federal Funding Opportunities

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

NIH: NIAID and NIDDK Research Opportunities for New and "At-Risk" Investigators to Promote Workforce Diversity (R01 Clinical Trial Optional) (PAR-23-275)

The purpose of this notice of funding opportunity (NOFO) is to encourage researchers from diverse backgrounds to work with their institutions to submit applications for research projects within the mission of either NIAID or NIDDK. This NOFO seeks to support either (a) a New Investigator (NI), who has not previously competed successfully for substantial, independent funding from NIH, or (b) an 'At-Risk' investigator, who had prior support as a PD/PI on a substantial independent research award and unless successful in securing a substantial research grant award in the current fiscal year, will have no substantial research grant funding in the following fiscal year. Application Deadlines: February 5, 2024; June 5, 2024; October 5, 2024; February 5; 2025; June 5, 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.

New Federal Funding Awards

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

Jorge Kizer, MD
Project Title: Role of IL-32 as a predictor and mediator of Premature Aging Phenotypes (PAP) in HIV infection
Sponsor: NIH subcontract via Centre Hospitalier De L'Université de Montréal
Activation Date: 9/12/2023

Duygu Tosun-Turgut, PhD
Project Title: Optimization of blood biomarker use in AD clinical trials
Sponsor: Alzheimer's Association
Activation Date: 9/14/2023

Theresa Allison, MD, PhD
Project Title: The impact of music on well-being after diagnosis with Alzheimer's disease or its related dementias
Sponsor: NIH
Activation Date: 10/5/2023

Michael Weiner, MD
Project Title: Alzheimer's Clinical Trials Consortium (ACTC)
Sponsor: NIH subcontract via Univeristy of Southern California
Activation Date: 10/5/2023

Beth Cohen, MAS, MD
Project Title: The Intersection of Tobacco and Cannabis: Impact on Tobacco Use Behavior and Cessation
Sponsor: TRDRP
Activation Date: 11/15/2023

Message from the Chief Executive Officer

Looking back at 2023, we saw many successes and opportunities for growth. Overall, we took several steps forward, and I am optimistic that we will continue the momentum in 2024. Most of all, I am struck by a sense of gratitude for the consistent collaboration of everyone at the SFVAHCS campus and the NCIRE staff for the dedication to our Mission: "To improve the health and well-being of Veterans and the general public by supporting a world-class biomedical research program conducted by the UCSF faculty at the San Francisco VA Health Care System."

The content in the Winter 2023 volume XXI is noteworthy. Thank you to the contributors: Duygu Tosun-Turgut, PhD, the details on the use of artificial intelligence in brain disorders is a remarkable read. Alison Rustagi, MD, PhD shared her work related to preventative care and primary care with interest in lung cancer screening. We appreciate their time and willingness to share their research.

NCIRE offers two generous retirement plans that represent a component of each employee's total compensation package. The Plans are audited annually; both the 403b and Defined Contribution plans. As of December 31, 2022, the combined Net Asset value of both plans represented $40.8M, ∼15% decrease from last year. The audit reports for the calendar year ending 2022 were issued at the end of October 2023. The reports with the Plan accounting and management practices, resulting in a "clean" audit.

I am pleased to share, **Grant highlights of the Fiscal Year 2023:**

111 total applications
- 48-Prime applications to federal sponsors
- 53-Subcontracts for federal awards
- 2-State (UCOP) applications
- 8-Foundations/Other

Fiscal Year 2022 - 116 applications

34 New Awards
- 11 NIH
- 1 DoD
- 22 Subcontracts on federal awards

Fiscal Year 2022 - 24 New Awards

17 New CRADAs
(industry research/awards)

Fiscal Year 2022 – 7 New CRADAs

In the fiscal year 2024 financial planning, there are fifty-five active federally-funded Investigators, compared to fifty-six federally-funded Investigators in 2023.

Reminder, NCIRE's Administrative Office will observe a Winter Closure, 12/21/23-1/1/24. We will re-open for business on Tuesday, January 2, 2024. NCIRE's Administrative Staff will not be available during this closure.

Thank you for taking time to read our Winter 2023 Newsletter. Please let me know if you have any questions or comments.

I sincerely wish a happy and safe holiday season to all.

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 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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