

CTSCconnections

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NOVEL CLINICAL RESEARCH

Partnering with the Alpha Stem Cell Clinic

IN EARLY 2018, UC Davis launched the Alpha Stem Cell Clinic (ASCC) with a nearly \$8 million grant from the California Institute for Regenerative Medicine (CIRM), joining a network of top California medical centers specializing in conducting stem cell clinical trials. To ensure that cutting-edge studies have the highest standard of care, the ASCC partners with the CTSC Clinical Research Center (CCRC). The CCRC provides a fully equipped outpatient facility staffed with highly trained registered nurses and a nurse practitioner to conduct experimental stem cell therapy protocols. In addition, the CCRC dedicated space within the clinic to house a telehealth portal and a specimen preparation room to foster stem cell research.



UC Davis Alpha Stem Cell Clinic team at the Institute for Regenerative Cures in Sacramento

“Partnering with the CTSC helped our Alpha Clinic to start treating patients just months after the CIRM grant was received,” says Jan Nolta, professor and co-principal investigator

of the Alpha Clinic grant and director of the UC Davis Stem Cell program and the Institute for Regenerative Cures. “We are grateful to have CTSC’s dedicated, experienced personnel

(Continued on page 2)

DIRECTOR’S MESSAGE

Ted Wun, M.D.

IN THIS ISSUE WE PROVIDE a sample of the breadth of clinical research activities of our center. As with most



Ted Wun, M.D.

organizations the greatest asset is our people. Erik Henricson, associate professor of physical medicine and rehabilitation,

is the faculty lead for the CTSC Regulatory Knowledge and Support program. Also featured is Daniel Nishijima, associate professor of emergency medicine – a graduate of the CTSC Mentored Clinical Research Training Program and former CTSC KL2 scholar. Exemplary in their academic pursuits and leadership roles, their experience speaks to the importance of formal training and mentorship – two pillars of the CTSC workforce development program.

We describe the Clinical Trials Office (CTO) and the CTSA Translational Innovation Network (TIN). Because the inception, design, conduct, analysis, and reporting of results has become more complex and rigorous, it indeed takes a village. The CTO provides the services necessary to conduct high quality trials and the TIN provides access to expertise through a national network for those who wish to conduct multicenter clinical trials. UC Davis investigators

(Continued on page 2)

DIRECTOR'S MESSAGE *continued from page 1*

can access the TIN to improve the competitiveness of their trial proposals and integrate ancillary studies that would not otherwise have been possible. Recently, one of our junior investigators opened a multicenter trial and serves as a site principal investigator – a unique research experience that might not have been available to her without the use of these resources.

We also seek to expand our engagement and collaboration

with community-based research efforts. One example is our support of Diana Miglioretti's work to develop the Sacramento Area Breast Cancer Registry. Engaging patients and other stakeholders from the start informed her research priorities and resulted in a project more attuned to the concerns of and relevant to patients while maintaining scientific rigor.

Finally, we highlight our partnership with the UC Davis Alpha Stem Cell Clinic. Funded by the California Institute for

Regenerative Medicine, this is one of five sites charged with conducting regenerative medicine clinical trials. Through this partnership, UC Davis investigators are at the forefront of cellular, gene augmentation, and regenerative medicine trials. Being housed within the CTSC Clinical Research Center allows a collaborative approach to ensure that this cutting edge research is conducted in a safe, compliant, and skilled clinical research environment. §

Partnering with the Alpha Stem Cell Clinic *Continued from page 1*

available to help our teams at UC Davis provide this new class of therapies.”

Several stem cell trials are currently underway and there are many more in the pipeline. Two examples of trials in progress are described below:

Immunotherapy for advanced nasopharyngeal carcinoma (NPC). Although rare in Europe and North America, NPC is a leading cause of cancer in Asia. Conventional chemoradiation therapies achieve a high rate of cure for localized disease, but metastatic spread has a poor prognosis. This phase III clinical trial evaluates supplementing standard therapy with an infusion of each subject's cytotoxic T lymphocytes that have been treated to target NPC cells. The trial follows a successful phase II trial that achieved the best published two-year survival rate (63 percent) in patients with advanced NPC. The current study is the world's first phase III T-cell cancer therapy trial and anticipated to enroll 330 patients from 29 hospitals in Asia and the U.S.

HOPE-2 for Duchenne muscular dystrophy (DMD). Novel therapies are an urgent need for DMD – a fatal genetic disorder that affects boys and young men. This phase II clinical trial will test allogenic cardiosphere-derived

cells, a unique population of cells containing cardiac progenitor cells that secrete exosomes and microvesicles. These fortified cells contain potent growth and secretory factors known to promote muscle regeneration, decrease inflammation, improve mitochondrial health, and help maintain or even improve critical cardiac and skeletal muscle function. About 84 patients will be recruited nationwide and randomized to receive four infusions of either treatment or placebo over a period of nine months.

One-stop shop

Mehrdad Abedi, principal investigator for the UC Davis Alpha Stem Cell Clinic and a specialist in bone marrow transplantation, applauds the ASCC-CCRC partnership. Everything needed for stem cell research – from collecting, manipulating, and storing cells in the UC Davis Good Manufacturing Practice (GMP) facility to safely administering experimental new treatments to patients in a controlled clinical setting – is now concentrated in one place.

“Having the necessary equipment, expertise and medical support together is a huge advantage in safely conducting research in new stem cell therapies,” says Abedi, professor in the UC Davis

Department of Internal Medicine and principal investigator for the NPC trial. “Before the Alpha Clinic, our pace was slowed by having to coordinate parts in disparate areas. Now many trials that were postponed are underway.”

Due to stringent regulations and trial complexity, stem cell research receives heavy scrutiny; many clinical research centers cannot conduct these studies because of the multiple barriers that exist. Abedi believes that the Alpha Clinic puts UC Davis Health in a good position to expand and eventually serve the entire UC system as well as smaller companies that are developing novel stem cell therapies.

Partnership generates excitement and excellence

According to Christopher Kain, manager of the CCRC, collaboration with the Alpha Clinic has created a lot of buzz among the staff members. The complexity and strict regulation of the clinical trials inspires nurses, support staff, and administrators to shift into high gear to meet the specialized requirements.

The ASCC and the CCRC co-created a policy to ensure patient

(Continued on page 8)

Facilitating the conduct of biomedical research

WITH MORE THAN 1,000 research studies conducted annually, UC Davis is a powerhouse of scientific investigation. To ease the path for researchers, the CTSC offers a host of services essential for conducting a successful clinical investigation. Erik Henricson, program director for CTSC Regulatory Knowledge and Support program, leads a highly trained team to provide research education, regulatory assistance, and study subject recruitment. This group aligns and integrates with the Clinical Trials Office to provide a comprehensive array of services to clinical research teams. CTSC clinical trial resources also include access to the Trial Innovation Network – a national network resource

to assist with multi-site clinical trials (see “Network Connects and Supports Investigators” article).

Research education

The vast collection of CTSC training and education resources includes a series of online training modules to develop competencies and “how-to” courses for staff and faculty researchers with different levels of experience. In addition, monthly brown bag lunches offer investigators from diverse fields the opportunity to learn about changes in the clinical research field.

Henricson is especially excited about a new course in the works. Aimed at honing the practical skills of junior investigators, he envisions

a graduate seminar using a combined approach of didactics and hands-on assignments tailored to student needs. The course will tackle such issues as developing a protocol, taking the next steps after obtaining a grant, and bridging the gap between basic and translational research.

“We are aiming to add another level that is more advanced compared to current course offerings to help develop the skills required for successful investigator-initiated projects,” adds Henricson. “The CTSC is fortunate to have the incredible resources of the university and UC Health to make such offerings possible.”

(Continued on page 4)

WELCOME

Erik Henricson

ERIK HENRICSON recently accepted a leadership position as director of the CTSC Regulatory Knowledge and Support program – a role that compliments his position as chair of the UC Davis Institutional Review Board committee for Social and Behavioral research. Henricson is also assistant professor and associate director for clinical research in the Department of Physical Medicine and Rehabilitation.

With training and experience in health system administration, public health, and clinical research, Henricson’s main research focus is the evaluation and treatment of children with neuromuscular diseases such as Duchenne muscular dystrophy (DMD). This field of research encompasses multidisciplinary projects involving genotype/phenotype characterization,

biomarker analysis, outcome measure development, person-reported and community outcomes, and clinical drug development. Since 2005, he has served as the co-chair of the Cooperative International Neuromuscular Research Group’s Duchenne Natural History Study, following about 450 children with DMD and their families worldwide.

As someone who benefited from CTSC services upon his arrival at UC Davis in 2006, Henricson seeks to ensure that clinical researchers can access resources that fully support their research. With firsthand knowledge of the logistical challenges that span clinical research, he is designing a program to help investigators prepare for and overcome the many obstacles that can impede progress. He leverages



Erik Henricson, Ph.D., M.P.H.

his passion for research excellence to encourage early career investigators and other clinical faculty to utilize CTSC resources.

Now a seasoned researcher, Henricson started out with a very different career goal. He grew up as a proud “Army brat” and dreamed of becoming a soldier. With an ROTC scholarship to Penn State, he leveraged his military training to try out for the U.S. Olympic Marksmanship Team – but defense budget cuts abruptly halted his military dreams and redirected his path into research. Although he didn’t make the trip to Barcelona, his kids relish the Olympic rings lapel pin he received at the team trials. Today, satisfied with his research career path, he cannot imagine his life any other way. §

Regulatory compliance

Clinical research is a highly regulated field. Investigators and their team members must navigate a convoluted path of rules, requirements, and regulations at the local, state, and federal level. Among the most widely known is a requirement for human subject protection by Institutional Review Boards (IRBs). IRB processes are complex and encompass a variety of applications, consent forms, reviews, and document approvals before human research can move forward.

In addition, federally funded research requires transparency and compliance with an array of regulatory requirements. For example, any study falling under the U.S. Food and Drug Administration or the National Institutes of Health definition of a clinical trial must register at ClinicalTrials.gov. This federal database serves as a repository for researchers to disclose details of study design, purpose, eligibility for enrollment,

outcome measures, and research results. And penalties for lack of disclosure can be steep – as high as \$13,000 per day and potential loss of the NIH funding!

Clinical studies also require a detailed budget and review of financial charges. Coverage analysis identifies all clinical items or services associated with a clinical trial, including identification of the financially accountable party. This process requires attention to detail and keen knowledge, and the CTSC provides training to ensure that research staff are prepared to meet the challenge.

Kate Marusina manages the CTSC Clinical Trials Office team of experts. Her staff offers services to support compliance with the state and federal regulations pertaining to clinical trials. Staff members advise researchers on budgeting, coverage analysis, study registration, and compliance with the requirements for IRB review. For self-serve assistance, the Clinical

Research Guidebook – a compendium of regulations and procedures to help investigators conduct studies at UC Davis – is now in a web-based wiki format (<https://bit.ly/2x9LQnw>).

Participant recruitment

Enrolling a sufficient number of qualified participants for clinical studies is a continual challenge. The old recruitment methods of fliers, snail mail, and newspaper ads are yielding to increasingly high-tech ways of finding potential study participants. Fred Stevenson, the CTSC clinical trials recruitment program manager, is dedicated to assisting researchers with subject recruitment resources.

“We’re living in a mobile world,” says Stevenson. He highlights the recently launched UC Davis Health Participate website (<https://www.ucdmc.ucdavis.edu/participate/index.html>) as a centralized institutional

(Continued on page 6)

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The new Participate portal connects patients and healthy volunteers to UC Davis clinical trials

Sacramento registry offers wealth of breast imaging data

THERE ARE MANY

unknowns about breast cancer screening, according to Diana Miglioretti, Dean's professor of biostatistics in the UC Davis Department of Public Health Sciences. Evaluating the effectiveness of new imaging modalities and personalizing screening strategies are just some of the issues that require large amounts of data.



Diana Miglioretti, Ph.D.

Enter the Breast Cancer Surveillance Consortium, a national network of registries that collects extensive information on breast imaging and outcomes to evaluate effectiveness and understand risk. Miglioretti is principal investigator of the Statistical Coordinating Center for the consortium, which currently has registries in six states across the United States.

With support from the UC Davis CTSC, she started a pilot project to add a new registry to the network – the Sacramento Area Breast Imaging Registry (SABIR). Eventually intending to collect breast imaging data throughout the greater Sacramento area, she started the project using three UC Davis facilities. “Data from the Sacramento area is especially important, as the population is more diverse than in the other network sites,” she says. “This registry will make a real contribution to the consortium.”

Many questions to probe

The field of breast cancer imaging is changing fast. New imaging modalities include digital breast tomosynthesis, breast magnetic resonance imaging, and whole breast ultrasonography. While touted as advances in the field,

Miglioretti points out that evidence of the risks and benefits of these methods does not yet support routine use for screening or surveillance. Current recommendations state that most women aged 50 to 74 years should be screened every two years, with some needing more frequent screening if they are

at increased risk. However, evidence-based research may alter guidance for breast cancer screening.

Should some high-risk women start screening at an earlier age? Can low-risk women be safely screened at intervals of every three years? Would some women – particularly those with high-density breast tissue – benefit from supplementary imaging methods? Miglioretti anticipates that consortium data will answer these and other related questions.

Complexities of data acquisition

A year into the SABIR project, her team enrolled 58,630 women in the registry and obtained data from these women on 245,503 breast imaging examinations, 8,166 breast biopsies, and 2,077 breast cancer diagnoses. Existing clinical data from examinations, procedures, and diagnoses from 2008-2018 were obtained from the UC Davis

mammography facilities in Sacramento, Folsom and Roseville.

When starting the project, Miglioretti's goal was simply to collect retrospective data from the UC Davis electronic medical record. But the task proved more complex than anticipated.

“Data collected for clinical purposes does not always mesh with what is needed for research,” she says. “Fortunately, the CTSC staff was there to help with the logistics. Having good technical support for these kinds of unexpected problems is critical.”

Future directions

According to Miglioretti, SABIR will pave the way for local investigators to mine the data for a myriad of issues related to breast cancer screening and surveillance in this region. For example, providers might use the data to identify groups that may need additional services.

Analysis of registry data can detect women who had a suspicious finding on screening mammography but did not return for follow-up. It would be worthwhile to characterize such at-risk populations: perhaps they are migrant farmworkers or women without health insurance, Miglioretti speculates. It may be possible to track down individuals with registry information or target such groups in the future for special outreach following mammography.

A future project could compare performance measures between mammography centers across the region. “It's critical that the preliminary work is done with the registry so that new researchers do not need to reinvent the wheel to obtain useful data,” says Miglioretti. “That way, one pilot project can make things easier for many translational studies.” §

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—Diana Miglioretti

WELCOME

Daniel Nishijima

DANIEL NISHIJIMA, former CTSC Mentored Clinical Research Training Program and KL2 scholar, accepted two key leadership roles at the CTSC – one as director of the CTSC Patient and Clinical Interaction program and the other as medical liaison to the CTSA Trial Innovation Network. In these complimentary roles, he leverages his clinical and research experience to advance the profile of UC Davis on the national stage.

During his years in early career development programs, he became intimately familiar with the services that the CTSC provides to investigators. Today, his leadership roles allow him to share his knowledge and encourage others with similar career aspirations.

As a clinician, researcher, and scholar, Nishijima appreciates



Daniel Nishijima, M.D., M.A.S.

the reward each facet of his career provides. The primary focus of his research lies in the management of traumatic and neurological emergencies. Currently, he serves as co-principal investigator of a multicenter pilot clinical trial evaluating tranexamic acid (an antifibrinolytic drug) in severely injured children. With a steadily increasing level of NIH funding at

the medical school over the past decade, Nishijima credits the CTSC and seeks to continue this trajectory. Specifically, he provides outreach and expertise to investigators and leads the charge to participate in large, multicenter clinical trials.

A native of the Big Island of Hawaii, Nishijima, and his wife Sabrina have two young boys (Milo – age 7, Andy – age 3). They enjoy spending time with family and friends, traveling and learning about new cultures, and playing all types of sports (especially baseball). Nishijima, managing his CTSC responsibilities remotely, will soon complete a 6-month sabbatical in the U.K. at the London School of Hygiene and Tropical Medicine. There he is learning new clinical trial methods and planning for a large-scale, multinational trial evaluating tranexamic acid in severely injured children. §

Facilitating the conduct of biomedical research *Continued from page 4*

location for patients and healthy volunteers to find ongoing clinical trials UC Davis. Deploying an attractive and navigable format, this user-friendly and informative website leverages StudyPages. “StudyPages is the Airbnb for clinical trials,” Stevenson adds. “It is a friendly, easy, and actionable way for community members to explore available trials.”

StudyPages allows the public to find trials using a variety of search categories, including disease, therapy, and location. The site provides easy-to-understand study descriptions with inclusion and exclusion criteria, as well as a link to contact the research team members (who are notified instantly when someone

expresses interest). This free resource is available to all UC Davis Health clinical research projects and provides a robust “login” access for researchers to manage volunteer interest, track contact, and document status. The CTSC is currently developing a version of StudyPages to help the UC Davis School of Veterinary Medicine recruit pets as research participants in veterinary clinical trials.

Serving the mission

Building research teams of the future to improve human health... By assisting investigators, scholars, and staff in the conduct of clinical research through education, regulatory support, and participant recruitment, the CTSC

provides access to key areas of expertise. In addition, the Clinical Trials Office provides investigators with access to a highly trained staff of clinical research coordinators experienced and trained in the complex clinical research environment and who can help monitor, mentor, and foster quality assurance through all phases of a clinical research protocol.

The UC Davis Participate web portal provides free resources to facilitate patient recruitment. §

Explore the Participate web portal at <https://www.ucdmc.ucdavis.edu/participate/>

National network connects and supports investigators

THE ROAD FROM a promising research concept to a multisite clinical trial can be long and arduous, according to Daniel Nishijima, the CTSC medical liaison to the CTSA Trial Innovation Network (TIN). The TIN was designed to provide a nation-wide resource devoted to smoothing that path. It is composed of three key elements: the more than 50 CTSA program hubs, three TIN centers, and a recruitment innovation center.

“The TIN supports investigators from diverse disciplines in many ways,” said Nishijima. “It is especially helpful for multisite clinical trials and studies.”

- *Supplying operational support.* From study design to participant recruitment and retention, the TIN provides expert input and support.
- *Centralizing institutional review.* Normally, protocols must be approved by the IRB at each investigational site. This can cause delays, Nishijima explains, as each IRB may have specific requests for protocol changes. The TIN organizes a single central IRB approval acceptable by all participating sites.
- *Matching study sites.* The TIN connects clinical trials with other

“The TIN supports investigators from diverse disciplines in many ways. It is especially helpful for multisite clinical trials and studies.”

—Daniel Nishijima

consisting of webinars, tutorials, and guides on evidence-based strategies. Topics include reducing disparities among study arms and using social media and a health system’s electronic medical records for recruitment.

- *Engaging stakeholders.* The TIN assists in communication with industry, patients, interest groups, and foundations.

The TIN also serves as a laboratory to study the research process. By collecting data on a variety of processes – such as clinical trial recruitment strategies – metrics are used to improve practices based on evidence.

“The goal of the TIN is to make the clinical trial process faster, more rigorous, and more cost-efficient,” says Nishijima, “I highly encourage UC Davis investigators to contact our team to take advantage of this incredible free resource.” §

Visit the CTSC TIN website at <https://www.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/tin.html>



Nishijima, an active physician/investigator who was a Mentored Clinical Research Training Program scholar and a CTSC KL2 scholar, serves as a resource for the TIN and has used it for his own clinical trials. He explains that the TIN helps remove roadblocks in many important ways, including the following:

- *Promoting participant recruitment and retention.* The TIN provides clinical trial recruitment and retention toolkits
- CTSA sites. UC Davis investigators can request such assistance, or conversely, be contacted by the TIN to join a current project in development.

Partnering with the Alpha Stem Cell Clinic *Continued from page 2*

safety and protocol integrity for stem cell administration. Included in the policy is a requirement for patients to be monitored by a nurse and either a nurse practitioner or the principal investigator (M.D. or D.O.) during the administration of the product and the immediate post-dose monitoring period, as defined in the written protocol. Such precautions are in place, says Kain, because of the extra degree of uncertainty surrounding patient response to the novel therapies.

“The Alpha Clinic trials are often the first time these treatments are being administered in humans,” explains Kain. “Everyone is working together to ensure patient safety, and so far, everything has gone great.” Kain adds that being part of this pioneering research has been a real morale booster for the CCRC staff. “This has put us right there on the forefront,” he says. “We are all proud to be part of something special like this.” §



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