DaCCoTA
DAKOTA CANCER COLLABORATIVE ON TRANSLATIONAL ACTIVITY
Spring 2021
Newsletter

UND pathology professor identifies a novel biomarker for cancer using 'digital pathology'


Sandeep Singhal

Sandeep Singhal, Ph.D., assistant professor in the UND School of Medicine & Health Sciences Department of Pathology, DaCCoTA Scholars awardee, and director of the IDeA Networks of Biomedical Research Excellence (INBRE) bioinformatics division, recently published a paper in *Communications Biology - Nature*, one of the world's leading journals in the natural sciences, on a potential novel biomarker for cancer.

The paper, which explored the use of digital pathology to profile the subcellular distribution of the transcriptional regulator protein Kaiso (ZBTB33) in breast tumors from American women, found new connections between Kaiso and the autophagy-related proteins LC3A and LC3B, "that are associated with features of the tumor immune microenvironment, survival, and race."

These findings make Kaiso a possible biomarker for breast cancer risk management and predictor of progression.

"Precision medicine is an emerging practice of medicine that combines genomics, big data analytics, and population health to produce targeted therapies and guide decisions made in regard to the prevention, diagnosis, and treatment of disease, for cancer in particular," explained Singhal. "Racial diversity is tied to both our genetics and our environment, which is why we attempt to link genetics, ancestry, and disease, particularly when race is described in terms of continent of origin."

This is why Singhal and his team sought to leverage "Artificial Intelligence-based automated image analysis algorithms" to the subcellular distribution of Kaiso in a racially diverse cohort of breast cancer patients.

"We found that both nuclear and cytoplasmic Kaiso proteins are associated with breast cancer outcomes, and each are independent predictors of overall breast cancer survival," Singhal said. "Specifically, patients stratified by nuclear and cytoplasmic Kaiso are enriched in cell stress and immune response, which differentially predict survival based on genetic ancestry."

The general findings presented in Singhal's study highlight Kaiso's potential as a predictive biomarker to guide future treatment decisions, particularly in the use of immunotherapy.

These results pave the way for future applications in prospective studies where profiles of nuclear and cytoplasmic Kaiso can be evaluated in clinical trials as both a predictive and prognostic breast cancer biomarker. And because the predictive value of Kaiso varies across racial groups, these findings further emphasize the need for the inclusion of diverse racial and ethnic groups in clinical trials.

"The future of this research is to identify the specific connections between pharmacogenetics and race/ethnicity and develop Kaiso as a predictive genetic biomarker of overall breast cancer survival and response to therapy," Singhal concluded. "The next stage of this project is to validate the role of Kaiso as a unique predictive genetic biomarker, characterize its functional linkage and association with tumor progression, genomic properties, features of the tumor microenvironment, and patient exposures through a racially diverse population with collaboration of different institutions."

by Brian James Schill

RAGE fuels NDSU, VA and Sanford research collaboration for antibodies to be used as therapeutic and diagnostic tools

The cell-surface molecule RAGE drives the search for antibody-based inhibitors in the lab of Dr. Estelle Leclerc, associate professor in pharmaceutical sciences at North Dakota State University.

Research in the lab of Dr. Estelle Leclerc (center), associate professor of pharmaceutical sciences at North Dakota State University, investigates monoclonal antibodies that could aid in future cancer treatments.

The Receptor for Advanced Glycation Endproducts (RAGE) is an immunoglobulin-like receptor involved in cancer. In several mouse models of human pathologies or diseases, antibodies against RAGE have shown promising results.

In research possible through a DaCCoTA Feasibility Award, Estelle Leclerc, Ph.D., NDSU School of Pharmacy; Thomas Wambach, M.D., Fargo, VA Health Care System; and Marcus Frohm, M.D., Sanford Health, are investigating RAGE subcellular localization in human melanoma tumors and pancreatic tumors.

In a second DaCCoTA Ready-to-Go research project, Leclerc and Daniel Tuvin, M.D., Sanford Health, are examining the efficacy of the RAGE antibodies in patient-derived xenografts. Dr. Leclerc's research collaboration with Dr. Tuvin includes obtaining tumor samples from consenting patients as the researchers examine the effectiveness of RAGE antibodies created in Leclerc's lab.

RAGE is a receptor that becomes expressed at higher levels in diseased tissues. When the RAGE receptor is turned on, deleterious messages are sent to the cells, leading to increased cellular damage.

In the past few years, Dr. Leclerc's research team developed biological tools that aim to block the action of RAGE. "These tools are antibodies, like those that are produced in our body to fight infection, and we have shown that these antibodies can reduce the deleterious effects of RAGE in certain conditions," said Leclerc.

Antibodies are very versatile tools that can be used as therapeutic, diagnostic, and research tools.

"We have shown that our monoclonal antibodies against RAGE were able to enhance the effect of chemotherapeutic agents used to treat melanoma and pancreatic cancer. The results of our research are important to the public because our research could lead to improved therapeutic approaches for treatment of cancer," said Leclerc. "These antibodies are unique and are only produced in our lab."

Experimental studies have identified that RAGE and its ligands are overexpressed in various diseases, including cancer, contributing to tumor growth and metastasis.

Targeting RAGE is a new therapeutic approach of interest to pharmaceutical companies. Dr. Leclerc's research group has generated a new monoclonal anti-RAGE antibody that reduces the growth rate of xenograft melanoma tumors. Results are encouraging and Dr. Leclerc's laboratory is currently developing new antibodies with improved therapeutic effects.

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Daniel Tuvin

Marcus Frohm

This research is published in the *International Journal of Molecular Sciences* found at DOI: 10.3390/ijms21207723 and DOI: 10.3390/ijms21238989.

"This has been a fantastic collaboration between multiple institutions and multiple disciplines fostered by the Dakota Cancer Collaborative," said Frohm. "In the age of immunotherapy and checkpoint inhibitors, the hope is that this research will lead to additional tools in our toolbox against tumor-specific signaling mechanisms for improved melanoma survival."

The DaCCoTA provides a network of mentors, experts, and Core Facilities to translate basic research into clinical research, spurring discoveries which ultimately may span from lab bench to bedside, resulting in more treatment options for physicians and their patients.

Dr. Leclerc has published more than 50 research manuscripts, reviews or book chapters, in journals such as *Nature*, the *Journal of Biological Chemistry*, *Biochemistry*, *Proceedings of the National Academies of Sciences*, and *J. Molecular Biology*. She joined NDSU Pharmaceutical Sciences in 2009, previously serving as a visiting scientist at the Scripps Research Institute and as a group leader in clinical chemistry at Children's Hospital in Zurich, Switzerland. More information about Dr. Leclerc and her research lab is found at www.ndsu.edu/pharmacy.

Dr. Wambach is a general surgeon at Fargo, VA Health Care System. He is a graduate of the University of North Dakota School of Medicine & Health Sciences and is board certified in Surgery by the American Board of Surgery.

Dr. Frohm is a specialist in skin cancer and skin surgery at Sanford. A graduate of the University of Michigan Medical School, with a residency at Mayo Clinic and a fellowship at the University of Michigan, he is certified by the American Board of Dermatology.

Dr. Tuvin, a specialist in cancer and general surgery at Sanford, is a graduate of I.M. Sechenov First Moscow State Medical University. He completed a residency at Waterbury Hospital, Waterbury, Conn., and a surgical oncology fellowship at Mount Sinai Medical Center in New York. He is certified by the American Board of Surgery.

By Carol Renner

Call for applications from the DaCCoTA Professional Development Core

The goal of the Dakota Cancer Collaborative on Translational Activity (DaCCoTA) is to stimulate growth of expertise and engagement in cancer-related clinical and translational research (CTR) in the Dakota region. The Professional Development Core is currently seeking proposals for the following funding mechanisms:

1) DaCCoTA Scholars Program - The purpose of this award is to stimulate the development of new CTR investigators. Awardees will receive salary support (50% FTE plus fringe) that guarantees a minimum of 50% protected research time for the project and up to $50,000 in annual research support for up to five years. The DaCCoTA will provide the first three years of funding, and the final two years will be funded by the applicant's home institution (contingent on adequate progress). The DaCCoTA Scholars Program offers both a basic and community engagement track, and early career faculty are encouraged to apply.

2) Clinical Research Opportunities Program - This program provides 20% release time (up to NIH cap) to community-practicing, hospital-based clinicians to allow for participation in training activities and collaboration in cancer-focused CTR. The goal of the program is to begin to shift translational cancer research in the Upper Midwest to an enterprise informed by the patient. It is not intended that supported individuals will become full-time, independent investigators with funding for their own research projects. However, it is expected that providing an understanding of CTR and tools for identifying unmet medical needs will allow trained clinicians to become effective collaborators. Individuals may collaborate with both clinical and non-clinical scientists to help identify unmet clinical needs that can become the focus of translational research efforts.

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Applications for each program can consider the multilevel manifestations of cancer (e.g. neurological, psychiatric), demographic risks, and social impact. Applications should focus on T2-T4 translational research, although T1 studies will be considered if there is a clear plan to progress to T2-T4.

Letters of intent were due March 15, 2021. Full applications will be invited from selected applicants and will be due April 15, 2021. The full RFAs are attached and available on the Professional Development Core website. For additional information, please contact Christian Burresh (Christian.Buresh@usd.edu). Please distribute this announcement to any interested parties.

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Save the Date – DaCCoTA Annual Symposium

The 2021 Virtual DaCCoTA Annual Symposium is scheduled for June 18, 2021, from 8 a.m. to 5 p.m.

- **Educational Opportunities (tentative topics)**
  - Clinical Trial Design
  - Mentorship
  - Demystifying the NIH Study Section
  - Use of Navigators in Cancer Care
  - Best Practices in Community Engagement
- **Poster Sessions**
- **DaCCoTA Awardee Presentations**
- **Networking Opportunities**
- **Additional information coming soon**

For more information about the DaCCoTA Annual Symposium, call 701.777.6875 or send an email to daccota@UND.edu.

DaCCoTA seeks poster abstracts for annual symposium on June 18

The DaCCoTA is currently soliciting poster abstracts for its 2021 Virtual Symposium, which will be held on June 18, 2021. Posters are expected to address cancer-related clinical and translational research. Posters can consider the multilevel manifestations of cancer (e.g., neurological, psychiatric), demographic risks, and/or social impact.

Posters that focus on T2-T4 translational research will be given priority, although T0-T1 studies will also be considered.

The submission deadline is April 1, 2021. More information is available at the DaCCoTA website: med.UND.edu/daccota.