

## Getting on Cancer's Nerves: Tumor Innervation as a Promising Therapeutic Target for Cancer Patients



Dr. Paola Vermeer is a cancer researcher at Sanford Health and a DaCCoTa Scholars awardee. She currently researches tumor innervation, particularly in ovarian cancer. She was recently awarded a BRCA grant from the University of Pennsylvania Basser Center, with a project entitled *“Defining the contribution of BRCA mutations to the presence and function of tumor-infiltrating nerves in ovarian cancer.”* The grant is a one-year, \$100,000 project to explore whether BRCA mutations potentiate high-grade serous ovarian carcinoma innervation, which would make them particularly vulnerable to nerve-targeted therapy. Positive outcomes will fuel future *in-vivo* studies to define if blocking intra-tumoral electrical activity attenuates tumor growth and improves survival of BRCA-mutated ovarian cancer.

Dr. Vermeer became interested in tumor innervation after she had a conversation with a colleague about the presence of nerves in tumors. Up until that point, she hadn't known that nerves were in the tumor microenvironment at all. She found this very exciting and started reading the few published articles on the topic. Then, she decided to stain some patient tumor samples for neuronal markers to see if her lab could identify nerves in the tumors. Sure enough, they could. This led to questions about how neurons are recruited to the tumor bed and what they do once they get there. This curiosity started around 2016 and has turned into the main focus of her research program.

***“The presence of intra-tumoral neurons is fascinating to me and shows how complex the tumor microenvironment really is. It makes sense to me that, similar to the vascular and immunological connections that tumors form with the ‘host’, that they would also elaborate neuronal connections to the host. The cancer is, after all, much like an organ (albeit a foreign organ) which requires these connections to remain viable. The same holds true for a tumor. Our job is to understand what the intra-tumoral neurons do in the context of the cancer,”*** says Dr. Vermeer.

Her lab has found that tumors release small vesicles called exosomes that induce tumor innervation. They have also discovered that most, if not all, solid tumors are innervated. In a recent review of innervation (Restaino & Vermeer 2021), she and her co-author detailed how the presence of nerves has been confirmed for breast, cervical, colorectal, esophageal, gastric, head and neck, melanoma, pancreatic, prostate, basal cell, and thyroid cancer.

Increased innervation contributes to worse patient outcomes, as densely innervated tumors are associated with increased metastatic rates. Her lab is working to determine the mechanisms by which the tumor-infiltrating nerves contribute to disease progression and therapeutic ways to block nerve recruitment.

As part of her DaCCoTA Scholars award, she—along with Austin Walz (senior research specialist), Anthony Restaino (University of South Dakota Stanford School of Medicine MD/Ph.D. student), and Jeff Barr (staff scientist)—has been working on three specific aims. 1) Characterize human ovarian cancer for tumor innervation. 2) Define if ovarian cancer exosomes promote tumor innervation. 3) Test the efficacy of a nerve growth factor neutralization in attenuating ovarian cancer innervation growth using mouse models.

She's already published some of their results in the journal *Cells* under the title *"Intra-Tumoral Nerve-Tracing in a Novel Syngeneic Model of High-Grade Serous Ovarian Carcinoma"*. Using a mouse model for high-grade serous ovarian carcinoma, they showed that regional sensory neurons innervate ovarian tumors.

Her lab's future research goals are to mechanistically define how intra-tumoral neurons contribute to disease progression, identify targets for therapeutic intervention and use mouse models to test their efficacy *in-vivo*. Ultimately, they would like to translate their findings into the clinic. While there are many targeted and immune-focused therapies available to cancer patients and some patients respond robustly, many fail to respond. She believes that until the neuronal component of the tumor is also 'disarmed', treatment failures will continue. This area has been largely ignored and she thinks once nerve-focused therapeutic interventions become a reality, researchers will make great strides in improving outcomes for cancer patients.

***"This is a very exciting time to be in cancer research. Our understanding of the intricacies of the tumor microenvironment grows by the day. Mechanistically unraveling the neuronal control of cancer will provide new therapeutic options for cancer patients. This is what my lab's sole purpose is,"*** concluded Dr. Vermeer.

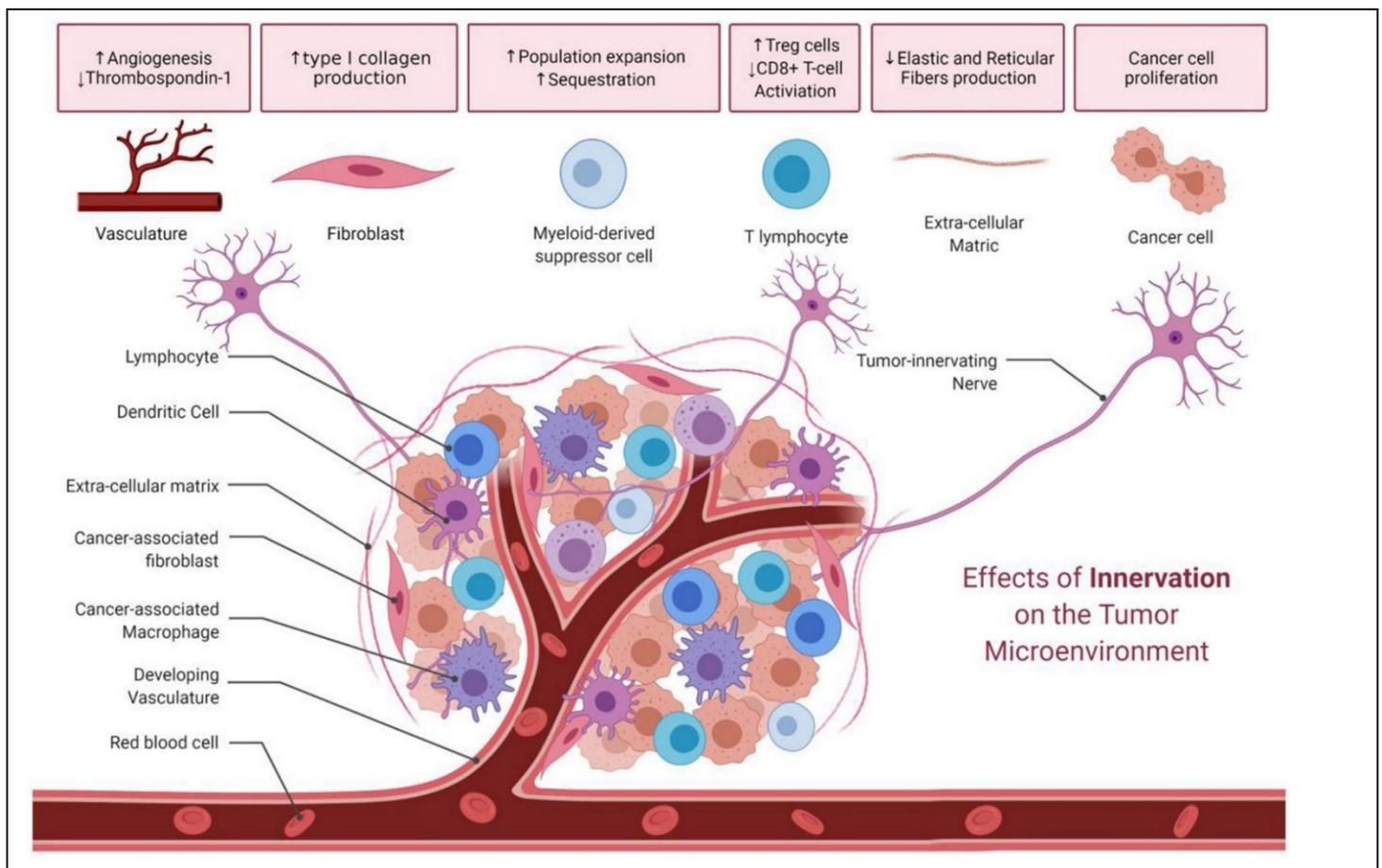


Figure 3 from **Neural regulations of the tumor microenvironment** (Restaino & Vermeer, 2021)

PMID: <https://pubmed.ncbi.nlm.nih.gov/35024571>

## Core Component Highlight: Clinical Resources and Facilities Core

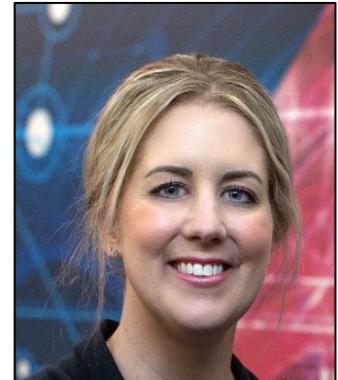
The overall goal of the Clinical Research Resources and Facilities Core is to provide synergy and expansion opportunities to the existing clinical services and technology cores available through partnering institutes, thereby fostering an ideal environment for the competitive execution of clinical and translational cancer research.

### Key Points

- Expand and facilitate access to patient samples from the Sanford Biobank and other hospital systems
- Facilitate access to large administrative patient data sets for all individuals associated with the DaCCoTA
- Provide a mechanism to efficiently propel clinical research projects
- Work closely with all DaCCoTA cores and investigators to expedite the design and execution of all clinical and translational research projects, serving as a centralized resource to facilitate innovative workflows and provide oversight for research involving human subjects
- Provide direction and oversight in the continued development and refinement of unified regulatory processes to streamline the efficiency of clinical research using multi-site centers through the Regulatory Oversight Committee (ROC)

### Services

- Project Management Support for DaCCoTA Applicant's and Awardee's Projects
- Regulatory Support for DaCCoTA Applicant's and Awardee's Projects
- Human Subjects & Clinical Research Education and Assistance throughout the lifespan of projects
- Assistance to Access Human Samples & Clinical Data



**Lora Black, RN, MPH, OCN, CCRP**  
Co-Core Director  
Sanford Research



**Kimberly Hammer, PhD**  
Co-Core Director  
Veterans Administration

*"The CRRFC is a critical component of the DaCCoTA CTR, ensuring timely access to resources for applicants and new investigators as they navigate the clinical research process."*

*-Lora Black*

*"CRRFC Project Managers utilize their knowledge and skills to guide clinical research throughout the project's duration. They provide superior customer service to facilitate execution and overcome barriers that arise. The CRRFC team is ready to help you achieve your research project goals."*

*-Dr. Kimberly Hammer*

## Recent Training Resources

Statistical Training Resources (<https://med.und.edu/daccota/berdc-resources.html>)

**Bite-sized Statistics**  
Lesson 6:  
Paired  
T-tests

**Advanced Power Analysis: Into the Weeds**  
BERDC Special Topics Talk 12

**Bite-sized Statistics**  
Lesson 7:  
Simple Linear  
Regression

**Multilevel Modeling for the Uninitiated**  
BERDC Special Topics Talk 13

**Bite-sized Statistics**  
Lesson 8:  
Multiple Linear  
Regression

**#5 Exploring R Packages with a Chipmunk: More Learning**

Dr. Mark Williamson  
Biostatistics, Epidemiology,  
and Research Design Core

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## Upcoming Calls for Applications

The goal of the Dakota Community Collaborative on Translational Activity (DaCCoTA) is to stimulate the growth of expertise and engagement in health-related clinical and translational research (CTR) in the Dakota region.

The **Professional Development Core (PDC)** will be seeking proposals for the following funding mechanisms:

- 1) DaCCoTA Scholars Program** – This program’s purpose is to stimulate the development of new CTR investigators. Applications are expected to **address health-related translational research of importance to North and South Dakota**. The program offers both a basic and community engagement track.
- 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 health-related CTR.

The **Pilot Projects Program (PPP)** will be seeking proposals for the following funding mechanisms:

- 1) Feasibility Pilot Grant Award** – This award is designed to allow a clinician/non-clinician team to form around a novel health-related hypothesis. Applications can consider the multilevel manifestations of health, demographic risks, and social impact.
- 2) Community Engagement Pilot Grant Award** – This award resembles the feasibility pilot grant but is specifically designed for projects addressing priority areas as determined by key community stakeholder groups.
- 3) Ready-to-Go Pilot Grant Award** – This award is intended for projects with existing significant preliminary data in support of a novel clinical/translational health-related hypothesis. These projects should ideally be ready for extramural submission within a year and/or be able to demonstrably improve health outcomes.
- 4) TREE Pilot Grant Award** – This award is design to provide funding for highly innovative projects that seek to translate promising epidemiological findings at the population level to relevant in vitro and/or in vivo experiments and/or the reverse, from in vitro and in vivo observations to a population setting.

RFAs will be released in **Fall 2022**. Full applications will be invited from selected applicants and will be due **Winter 2022**.

## Recent Events

- March 2022
  - **NIH R21 Mock Peer Review**, hosted by the PDC (March 28<sup>th</sup>)
- April 2022
  - **Core Training Event: Biostatistics Resource Overview**, hosted by the Biostats Core (April 27<sup>th</sup>)
- May 2022
  - **Innovation and Commercialization in Research**, hosted by the PDC (May 18<sup>th</sup>)
  - **DaCCoTA Grant Writing Program**, hosted by Dr. Barry Milavetz (started May 18<sup>th</sup>)
  - **DaCCoTA Core Training Event: Defining & Determining Human Subjects Research**, hosted by the CRFCC (May 25<sup>th</sup>)

## Upcoming Events

- June 2022
  - Core Training Event: *Research with Native American Communities*, hosted by the CEOC (June 15th)
- July 2022
  - Core Training Event: *R03, 15, 21 Awards*, hosted by the PDC (Date TBD)
- August 2022
  - Core Training Event: *Things to Consider with Project and Application Development*, hosted by the CRRFC (Date TBD)

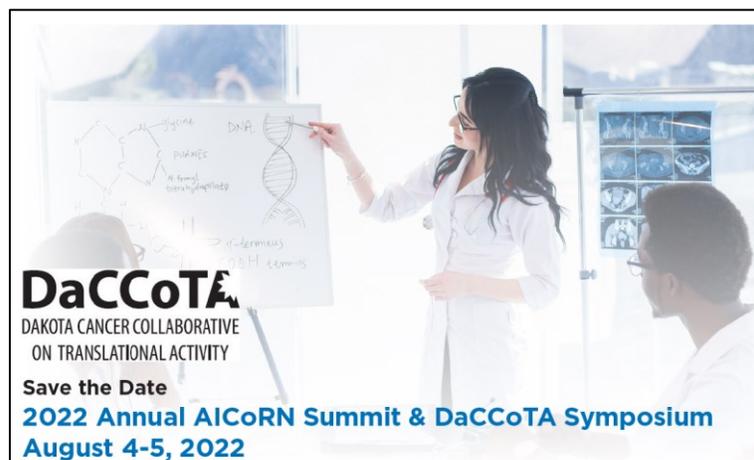
## Annual Symposium

The American Indian Collaborative Research Network and Dakota Cancer Collaborative on Translational Activity invite healthcare providers and other stakeholders interested in research to join the conversation and participate in this year's summit and symposium.

**Sanford Center -Sanford Health, Sioux Falls, SD (Virtual Option Available)**

Check the DaCCoTA Symposium Website for updates as additional information becomes available:

<https://med.und.edu/daccota/symposium.html>



Registration is now open: <https://app.smartsheet.com/b/form/a406f3d205b44330b05df48edbde3f0b>

<p><b>AICoRN (American Indian Collaborative Research Network) Summit Events</b></p> <ul style="list-style-type: none"> <li>• Keynote Speakers <ul style="list-style-type: none"> <li>○ Dr. Donald Warne, Dr. Jeff Hostetter, Dr. Dan Petereit and others</li> </ul> </li> <li>• Educational Opportunities</li> <li>• Research Priorities with Community Engagement <ul style="list-style-type: none"> <li>○ Join our afternoon participatory event facilitated by CHAD</li> <li>○ Inviting Tribal and other rural and underserved stakeholders</li> </ul> </li> </ul>	<p><b>DaCCoTA Symposium Events</b></p> <ul style="list-style-type: none"> <li>• Educational Opportunities <ul style="list-style-type: none"> <li>○ Introduction to Clinical-Translational Research - 2 Part Series</li> <li>○ An Awardee's Account of the DaCCoTA</li> <li>○ Implementation &amp; Delivery of Research Care</li> <li>○ Industrial Navigation</li> <li>○ Engaging American Indian Communities</li> </ul> </li> <li>• Poster Sessions <ul style="list-style-type: none"> <li>○ Open to graduate students, postdocs, and faculty</li> <li>○ Preference will be given to posters that address clinical and translational research of all specialties</li> </ul> </li> <li>• DaCCoTA Awardee Presentations</li> </ul>
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