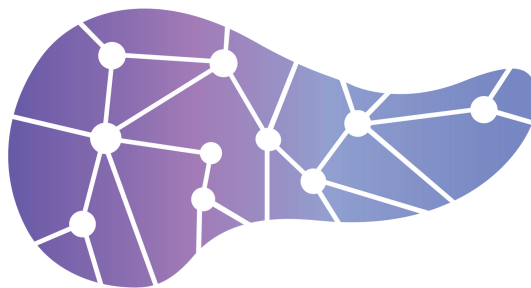


NDSU PHARMACEUTICAL
SCIENCES



COBRE

PANCREATIC CANCER
FOUNDATIONAL AND TRANSLATIONAL RESEARCH
SYMPOSIUM
NORTH DAKOTA STATE UNIVERSITY

**THURSDAY,
JULY 20, 2023**

9 AM - 7 PM

**HARRY D. MCGOVERN ALUMNI
CENTER**

NORTH DAKOTA STATE UNIVERSITY



www.ndsu.edu/centers/pancreaticcancer/

Sponsored by the NDSU Center for Diagnostic and Therapeutic Strategies in Pancreatic Cancer under the Center for Biomedical Research Excellence (COBRE) program of the National Institute of General Medical Sciences (2P20GM109024)

Thank you for participating in the Pancreatic Cancer Foundational and Translational Research Symposium at North Dakota State University. It is an opportunity to explore new research directions and learn from exceptional leaders at the forefront of research in pancreatic cancer diagnosis and drug delivery treatments.

Sanku Mallik

Professor of Pharmaceutical Sciences, College of Health and Human Sciences
Director, NDSU Center for Diagnostic and Therapeutic Strategies in Pancreatic Cancer

Sathish Venkatachalem

Associate Professor of Pharmaceutical Sciences, College of Health and Human Sciences
Co-Director, NDSU Center for Diagnostic and Therapeutic Strategies in Pancreatic Cancer



SYMPOSIUM AGENDA

THURSDAY, JULY 20

8:30 a.m. Breakfast / Registration – Harry D. McGovern Alumni Center Atrium
1241 N. University Drive, Fargo, North Dakota

Session 1, Alumni Center Atrium - Presentations in Alumni Center Reimers

- 9:00 a.m. Welcome and Opening Remarks
NDSU Provost, David Bertolini
Colleen Fitzgerald, NDSU Vice President for Research and Creative Activity
- 9:30 a.m. “Remodeling the Lung Tumor Microenvironment with Locally Administered Immunochemotherapies”
Sandro da Rocha, Ph.D., Professor, Director of Pharmaceutical Engineering, Virginia Commonwealth University
- 10:15 a.m. Break
- 10:45 a.m. “Targeting Transcriptional Reprogramming for Cancer Therapy”
Igor Roninson, Ph.D., Professor, Director, Center for Targeted Therapeutics
College of Pharmacy, University of South Carolina
- 11:30 a.m. “Cell and Lattice-Based Modeling for Cancer Biology”
Luke Theogarajan, Ph.D., Professor and Vice-Chair, Electrical and Computer Engineering, University of California Santa Barbara
- 12:15 p.m. Lunch / Poster Session

Session 2, Alumni Center Reimers Room

- 1:45 p.m. “Development of long-lasting nanozymes for pathogen deactivation”
Sudipta Seal, Ph.D., Professor and Chair, Materials Science and Engineering, University of Central Florida Orlando
- 2:30 p.m. “Engineering of soft nanomaterials for combination cancer therapy”
Tatiana Bronich, Ph.D., Associate Dean, Bouvé College of Health Sciences, Dean, School of Pharmacy and Pharmaceutical Sciences, Northeastern University
- 3:15 p.m. Break



3:45 p.m. “Current Status of Early Detection of Pancreatic Adenocarcinoma “
Randal Brand, MD, Professor of Medicine, Director, GI Malignancy Early
Detection, Diagnosis & Prevention Program, University of Pittsburgh Medical
Center

4:30 p.m. Closing Comments
Jagdish Singh, Professor and Chair, NDSU Department of Pharmaceutical
Sciences

NDSU Harry D. McGovern Alumni Center Atrium - Presentation in Reimers

5:30 p.m. Reception – Alumni Center, 1241 N. University Drive, Fargo, North Dakota

6:30 p.m. Dinner

7:00 p.m. “Immunosuppression in pancreatic cancer”
Michael A. (Tony) Hollingsworth, Ph.D., Associate Director for Basic Research
Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center
Omaha

FRIDAY, JULY 21

Alumni Center Reimers Room

8:30 a.m. Breakfast

8:30 a.m. “Antibody-Drug Conjugates as Targeted Cancer Therapies: Recent
Developments in Linker and Conjugation Chemistries”
Pradeep Dhal, Ph.D., Senior R & D Director within Early Development
Synthetics Platform organization, Sanofi Global Research and Development
Bridgewater, New Jersey

9:15 a.m. Informal discussion with Dr. Dhal and students on industrial research careers

9:15 a.m. Q & A with Dr. Dhal

9:45 a.m. Break

10:00 a.m. "Communicating Effectively: Intent, Impact and Avoiding Pitfalls"
Informal discussion with Kristine Paranica (NDSU Ombudsperson)

11:00 a.m. Lunch (grab-n-go), Atrium



PRESENTER ABSTRACTS

Remodeling the Lung Tumor Microenvironment with Locally Administered Immunochemotherapies

Sandro da Rocha, PhD

Professor, Director of Pharmaceutical Engineering, Virginia Commonwealth University, Richmond, Virginia



In this work, we discuss how pulmonary administration of immunotherapies can safely shift the balance of tumor-associated macrophages (TAMs) in the lung tumor microenvironment (TME) away from tumor tolerance. We also discuss how such a shift supports chemotherapies that are well tolerated upon local lung administration.

We present these results in the context of an immunocompetent model of osteosarcoma (OS) lung metastases (OSLM). We also discuss the potential of nanomedicines and inhalation formulation approaches developed in our group for local lung delivery of such therapies.

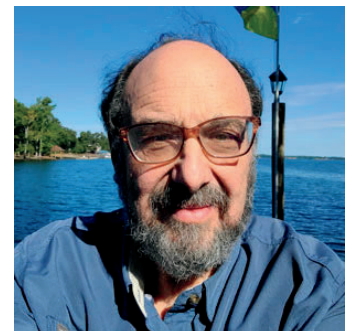
This work is clinically significant as, for the first time, it shows the potential benefit of combination immune-chemotherapy locally administered to the lungs for treating lung tumors in general and OLSM in particular. No new treatments have been approved in the past three decades for OLSM, despite the low survival rates. Most OS patients present micrometastases at the time of first diagnosis, and lung disease is the major cause of death for those that develop gross lung metastases.

This work is scientifically significant as we first show how the lung TME is being remodeled in terms of both the immune infiltrates and tumor cell phenotypes upon local pulmonary administration of such combination therapies. For the first time, we also address the safety profile of locally administered CSF-IRis to the lungs, as well as their combination with chemotherapies and nanomedicines that can be used to enhance their effects further.

Targeting Transcriptional Reprogramming for Cancer Therapy

Igor Roninson, PhD

Professor, Director, Center for Targeted Therapeutics, College of Pharmacy, University of South Carolina, Columbia, South Carolina



The plasticity of tumor cells, a key cause of treatment failure, allows them to adapt to different therapy types and grow in a heterologous (metastatic) environment. Tumor plasticity is based on the ability of tumor and stromal cells to change their program of gene expression (transcriptional reprogramming). We are studying the role of CDK8/19 Mediator kinase, a regulatory protein that mediates transcriptional reprogramming during embryonic development, in cancer therapy resistance and metastasis. Selective CDK8/19 inhibitors prevent the development of drug resistance and suppress tumor growth under conditions that require transcriptional reprogramming. We will discuss the transcriptomic effects of CDK8/19 inhibitors and their impact on advanced prostate and breast cancers.



Cell and Lattice-Based Modeling for Cancer Biology

Luke Theogarajan, PhD

Professor and Vice-Chair, Electrical and Computer Engineering, University of California, Santa Barbara, California

The use of in silico modeling to understand the evolution of cancer has steadily increased due to the increased availability of computing power. A particular class of models used in statistical physics- The Potts model is increasingly used in this arena. In this talk, I will review the basic ideas of cellular Potts models and how they apply to cancer modeling. I will also present some ideas for speeding up the simulations and increasing the scale to include 10^6 to 10^9 cells using some new computational hardware we are exploring in my lab.



Development of long-lasting nanozymes for pathogen deactivation

Sudipta Seal, Ph.D.

Professor and Chair, Materials Science and Engineering, University of Central Florida, Orlando, Florida

COVID-19 has shaped up to be one of the defining challenges of our lives. Among the primary modes of spread is surface-to-surface contamination. Under these circumstances, the shortcomings of traditional chemical agent-based disinfectants got more pronounced. Furthermore, a lack of regenerative properties and the short-duration activity of traditional disinfectants impacted the efforts to contain the spread. Here we report a novel self-cleaning antiviral coating based on metal/oxide nano-surfaces. In addition, it has also shown antiviral properties against a range of viruses, including SARS-CoV-2, Rhinovirus, La Crosse virus, Vaccinia virus, Vesicular Stomatitis virus, Parainfluenza virus, and Zika virus. Finally, we have also used AI/ML for new materials designed to combat infectious diseases.



Engineering of soft nanomaterials for combination cancer therapy

Tatiana Bronich, PhD

Associate Dean, Bouvé College of Health Sciences; Dean, School of Pharmacy and Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts

We successfully developed a novel platform for drug delivery based on nanoscale-size polymeric gels. The nanogels are manufactured through a self-assembly process, which involves the formation of a cross-linked polyion core micelle coated by inert PEG chains. The resulting nanogels are water-swollen, have very low buoyant density, and are practically non-adhesive, which may diminish off-target side effects during their delivery to tumors. Nanogels are unique because they can simultaneously incorporate water-soluble and anti-cancer drugs. Nanogels are versatile and can be engineered to produce desired payloads of their therapeutic cargos, drug release profiles and possibly modify the PK, biodistribution, safety, and efficacy of delivered anti-cancer therapeutics. The potential application of such nanogels as carriers for multidrug delivery will be discussed.





Current Status of Early Detection of Pancreatic Adenocarcinoma

Randall Brand, MD

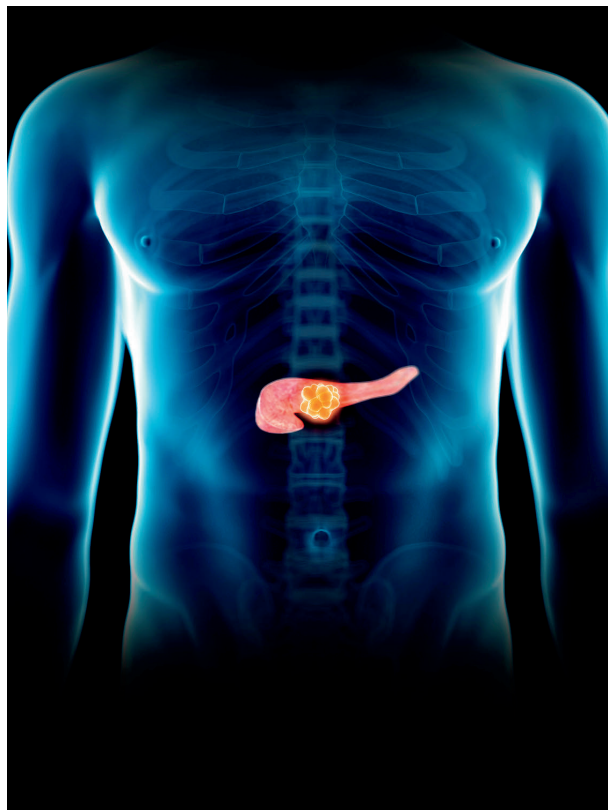
Professor of Medicine

Director, GI Malignancy Early Detection, Diagnosis & Prevention Program,
University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania



Pancreatic adenocarcinoma (PDAC), with an overall 5-year survival of 12%, is the 3rd most common cause of cancer deaths in the United States, despite accounting for only 2% of all malignancies. Only a minority of patients (~11%) are diagnosed with "localized" disease (I or IIA), which has a 5-year survival rate of about 40% in the setting of a node-negative, margin-negative pancreatic resection. An obvious strategy for improving the dismal survival would be to detect PDAC when localized and thus at a more curable stage. Since screening the general population for PDAC is not feasible, current efforts have focused on identifying a subset of the people at an increased risk for PDAC development. Unfortunately, only up to 25% of individuals who develop PDAC are candidates for pancreatic cancer surveillance. About 10% are individuals with a strong family history or a combination of family history and germline mutations associated with the risk of PDAC development. The other ~15% are individuals with cystic neoplasms of the pancreas, including IPMNs and MCNs. The inability to predict the malignant transformation of mucinous cysts and thus identify the cysts that should be surgically removed requires appropriate surveillance. Despite developing multiple consensus guidelines on managing cystic lesions, it is still challenging to determine which mucinous cysts will undergo malignant transformation.

My presentation will define the population of individuals at an increased risk for developing pancreatic cancer and are candidates for pancreatic cancer surveillance. I will also describe current strategies for pancreatic cancer surveillance in these high-risk individuals with a significant focus on approaches and outcomes. Finally, areas requiring additional research for pancreatic cancer surveillance will be highlighted.





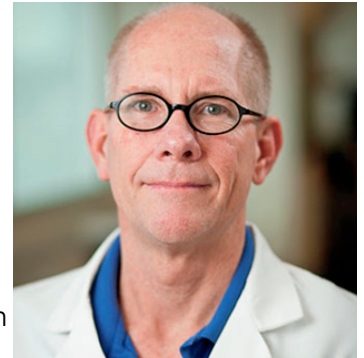
PRESENTER ABSTRACTS

Immunosuppression in pancreatic cancer

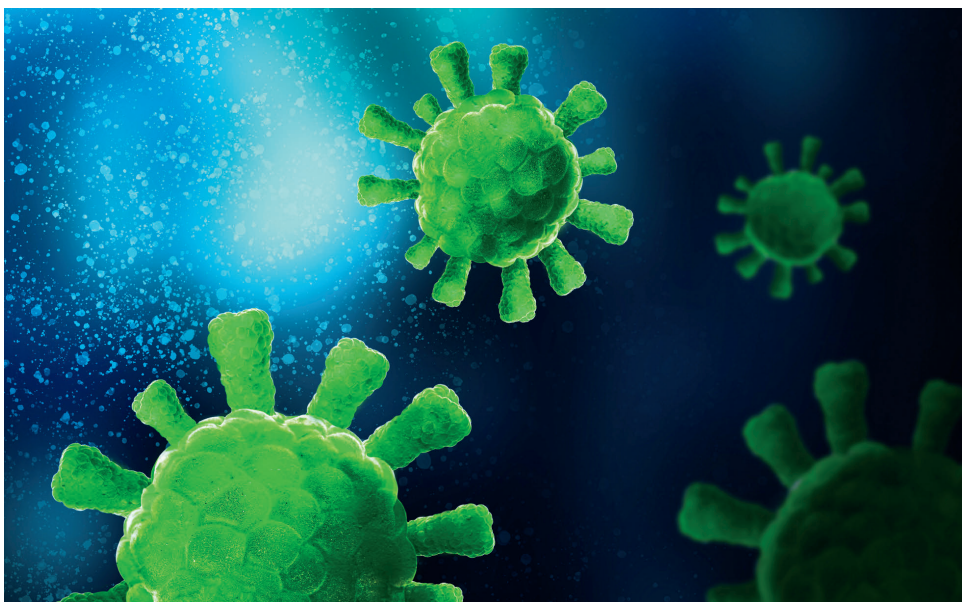
Michael A. (Tony) Hollingsworth, Ph.D.

Associate Director for Basic Research

Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center,
Omaha, Nebraska



One characteristic of pancreatic cancer that remains unexplained is the fact that shortly after diagnosis, many patients experience a decline in performance status and overall health, leading to rapid death, compared to many other cancers. Although this has been attributed in part to late diagnosis, many distinct paraneoplastic features of pancreatic cancer contribute to this rapid decline. Cachexia, pain, blood coagulation events, and depression are widely reported to accompany the progression of pancreatic cancer. Immunosuppression and inflammatory conditions also contribute to tumor progression; however, the role of these in acute events that lead to death (e.g., systemic immunosuppression) is less well studied. We have conducted 161 rapid autopsies on patients that died of pancreatic or related cancers over the past 22 years, and a review of the acute causes of death in these patients revealed a surprising finding – that approximately 65% of pancreatic cancer patients die from acute bronchopneumonia (viral and fungal), and another 3% die from sepsis. In addition, 25% of patients that die from other acute causes show evidence of bacterial or fungal infections in the lung. Notably, there was a previous report in 1995 that evaluated the results of 154 consecutive autopsies for pancreatic cancer patients from 1952-1992 at the Medical College of Ohio (prior to the advent of current therapies), which reported that acute causes of death in these patients were due to bronchopneumonia (~60%) and sepsis (or severe infection) (~10%) at percentages that are nearly identical to our findings. These authors concluded, “The most immediate causes of death....were bronchopneumonia, thromboembolic disease, and sepsis, as well as acute hemorrhagic erosive gastroenteritis or stress ulcer.” Taken together, these studies suggest two significant findings: (1) most patients with pancreatic cancer die because of and with opportunistic infections (in our series the vast majority of these are viral), and (2) the acute causes of death with pancreatic cancer have not been affected by different therapies that have been deployed over the past 70 years. We propose that pancreatic cancer causes profound immunosuppression both locally and systemically that leads to both failures to reject the tumor and inability to eliminate opportunistic infections that lead to the acute demise of the patient. For this presentation, I will discuss our characterization of immune cells from tumors, blood, and spleens of pancreatic cancer patients with an emphasis on the nature of immunosuppression enforced by the tumors.





PRESENTER ABSTRACTS

Antibody-Drug Conjugates as Targeted Cancer Therapies: Recent Developments in Linker and Conjugation Chemistries

Pradeep Dhal, PhD

Senior R & D Director within Early Development Synthetics Platform Organization
Sanofi Global Research and Development, Bridgewater,
New Jersey



Antibody-drug conjugates (ADCs) have become an essential class of targeted anti-cancer therapies. During the past decade, significant progress has been made in this therapeutic modality, with 12 approved drugs and more than 100 ongoing clinical trials. ADCs combine the superior targeting properties of antibodies with the cell-killing properties of highly cytotoxic drugs (payload). However, despite their clinical successes, challenges remain to improve the therapeutic indices of ADCs, i.e., greater efficacy with significantly reduced off-target toxicity. Accordingly, significant research efforts are underway to discover and develop novel linkers, payloads, and site-specific bioconjugation to obtain ADCs with homogenous composition, improved stability, multi-targeting, and optimal incorporation of payloads. Followed by a brief overview of the current state of ADC research and development, this presentation will highlight the progress towards the strategy of discovering multivalent drug linkers, improving the hydrophilicity of payloads, and site-specific bioconjugations to develop next-generation ADCs with examples from the presenter's lab.

Communicating Effectively: Intent, Impact and Avoiding Pitfalls

Kristine Paranica, J.D.

Organizational Ombuds at NDSU; Certified Transformative Mediator™; Certified Conflict Coach



Success in our personal and professional relationships depend on our ability to communicate well – to listen, respond, and engage. In professional working relationships, communication is key to ensuring messages are clear so we have common understandings. There are many obstacles in our way, including cultural miscommunication, misunderstandings of intent and impact, lack of clear communication, and so forth. In this workshop, we will identify some common pitfalls and learn how to be more effective in our communications.



POSTER PRESENTATIONS / ABSTRACTS

Computational and theoretical fluid mechanics modeling for transport in dense tumors

Mohammad Mehedi Hasan Akash and Saikat Basu

Department of Mechanical Engineering, South Dakota State University, Brookings, SD

We propose a physiologically realistic numerical model to quantitatively characterize perfusion through the dense extracellular matrix of solid tumors, as a function of tumor packing fraction and vasculature shapes. Incorporating electrohydrodynamic effects that impact the transport regimes, the model uses sinusoidal and imaging-based geometries for the tumor-adhering blood vessels. The subsequent computational simulations measure the spatio-temporal fluctuations for constituent volume fractions of high and low viscosity plasma, RBCs, and WBCs in the tumor vasculature, while recording plasma pressure and velocity at endothelial gaps. The data is then imported to a convection-diffusion based reduced order mathematical model for plasma penetration into the tumor extracellular space. The percolation rates are seen to vary inversely with the intra-tumoral diffusion distance, thus providing insights into the complex fluidic transport mechanism. Validating experimental designs in microfluidic setups and cell culture derived tumor spheroids embedded in fluidic domains are also discussed.

Targeting TNBC tumor using hypoxia-responsive nanoparticles containing drug with a synergistic effect

Shubhashri Ambhore, Connor Edvall, Narendra Kale, Sanku Mallik

Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

Triple-negative breast cancer (TNBC) cells do not express estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC is more aggressive due to increased metastasis, high recurrence rate, and a limited number for targeted therapies than other subtypes of breast cancer. Doxorubicin is an anticancer drug with serious side effects. Napabucasin (NAPA) is a STAT-3 inhibitor undergoing clinical trials as an adjuvant therapy for solid tumors. We hypothesized that NAPA would decrease the stemness and increases the effectiveness of Doxorubicin (Dox) in killing TNBC cells under hypoxia. Using the MDA-MB-231 TNBC cells, we observed a synergistic effect of NAPA and DOX in regulating cell proliferation under Normoxia (21% oxygen) and hypoxia (0.2% oxygen). Interestingly, the synergistic effect was higher in hypoxia compared to Normoxia. In addition, we observed increased neuropilin-1 (NRP-1) receptor expression on MDA-MB231 and patient-derived TNBC cells under hypoxia. Overall, NAPA and DOX show promising effects in synergistically regulating cell proliferation of MD-MB-231 in synergistic manner. We propose to prepare NRP-1 targeted hypoxia-responsive polymersomes to deliver NAPA and DOX selectively in the hypoxic TNBC cells.

Correlating polymer degradation and drug release kinetics with the effects of paclitaxel-loaded PLGA nanoparticles on pancreatic cancer spheroids

Rishabh Bahl, Lara Meinzingerz, Annika Deppe, Haley Jahnke, Camryn Blackwell, Joshua Reineke

Department of Pharmaceutical Sciences, South Dakota State University, Brookings, SD

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive and resistant form of cancer characterized by excessive extracellular matrix (ECM), which forms a physical barrier and reduces neovascularization. Paclitaxel (PTX) and gemcitabine (GEM) are leading therapies for the treatment of PDAC. However, PTX is a substrate for P-glycoprotein (P-gp) whose expression has been demonstrated in pancreatic cancer cells. Nanoparticle-based delivery can circumvent P-gp efflux. This study aims to understand the effects PTX-loaded PLGA nanoparticle (PTX-NP), in a desmoplastic 3D co-culture, as a function of its polymer degradation (evaluated by gel permeation chromatography) and intra and extra cellular drug release. The spheroids initially averaged 0.048 ± 0.012 mm³. Untreated spheroids showed no debris, whereas free PTX showed more debris compared to GEM after 72hrs of exposure. PTX-NP under stirring were toxic even at lower strengths as indicated by the dense debris formation and reduction in volume. PTX-NP exhibited partial release in DMEM (46.55% released by 2.5 hours).



Mentoring Perceptions during COBRE Phase I

Dan Cernusca

Department of Pharmacy Practice, North Dakota State University, Fargo, ND

The mentoring perceptions of COBRE stakeholders (Junior Investigators, Internal Mentors, Graduate Students and to Administrators) was monitored with online surveys administered on an annual base. The Junior Investigators' perception of their perceived internal mentoring quality was on average consistent across the 4 years covered in this study and relatively high with annual mean scoring values between 5.38 and 5.65 (7 - high). Both the annual mean scores and the minimum individual mean scores were higher for the external mentoring quality when compare to the internal mentoring with mean annual scoring values between 5.80 and 7.00. In addition, Junior investigators were able to act as valuable mentors for their graduate students and that the quality of their mentoring was consistent across the 4 years covered in this study with annual mean scores varying from 6.19 to 6.69, very close to 7, the highest level of evaluation scale.

Intestinal chemoattractant signals recruit ILC3s through VIPàVPAC1 signaling

Jessica DeCuyper and Glenn Dorsam

Department of Microbiological Sciences, North Dakota State University, Fargo, ND

Understanding the mechanism of type 3 innate lymphoid cell (ILC3) recruitment to the intestines would aid in the development of therapeutic drugs for colorectal cancers and inflammatory bowel diseases. The enteric nervous system delivers the gut neuropeptide, vasoactive intestinal peptide (VIP), to the intestines. VIP then binds to its receptor VIP/pituitary adenylate cyclase activating polypeptide (VPAC1) that recruits ILC3s to the intestinal lamina propria. VIP- and VPAC1-deficient 2-week-old prenatal mice have normal ILC3 recruitment, but in 8-week-old postnatal mice there is a loss of ILC3s in the intestines causing gut microbiota dysbiosis. It is unknown whether chemoattractant signals from intestinal epithelial cells (IECs) recruit ILC3s to the intestines in postnatal mice, or whether gut microbiota dysbiosis occurs in VIP- or VPAC1-deficient prenatal mice. We hypothesize that chemotactic signaling recruits ILC3s to IECs through VIPàVPAC1 signaling in postnatal, but not prenatal mice, to regulate gut microbiota homeostasis. We will take mouse fecal samples every other week from 2-8 weeks and subject them to 16S rRNA sequencing. Mouse intestinal tissues will be harvested for enumeration of ILC3 numbers through flow cytometry. As mice age up from 2-8 weeks, the mice will have greater gut microbiota dysbiosis. In prenatal mice, ILC3 recruitment should be equal in wild-type and knockout mice, but declines by 8 weeks old. This research is expected to provide a better understanding of how VIPàVPAC1 signaling works with ILC3 recruitment to aid in gut microbiota homeostasis and intestinal barrier defense against pathogens.

Synergistic Effects of Two Drugs on Triple-Negative Breast Cancer Spheroids

Connor Edvall(1), Narendra Kale(1), Jiyen Mohammad(1), Daniel M. Tuvin(2), Venkatachalem Sathish(1), Sanku Mallik(1)

(1) Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

(2) Sanford Broadway Clinic, Fargo, ND

Triple-negative breast cancer (TNBC) is challenging to treat and lacks the estrogen receptor, progesterone receptor, and HER2 protein expressions. TNBC tumors become low in oxygen or hypoxic due to rapid growth. Hypoxia-induced genetic alterations form cancer stem cells, making treatment increasingly difficult. To target these tumors and hypoxic regions, iRGD, an NRPI targeting peptide, and a hypoxia-responsive polymer are incorporated into polymersomes with encapsulated doxorubicin (DOX) and all-trans retinoic acid (ATRA). Due to NRPI upregulation in hypoxic cancer cells, the iRGD peptide helps the polymersomes penetrate solid tumors and reach the hypoxic niches. ATRA was chosen to reduce the stemness of the cells, and to kill the cells, DOX was chosen. Encapsulated DOX with ATRA had significantly higher cytotoxicity than the encapsulated drugs alone and free drug combination. In addition, the combination had a higher spheroid size reduction than the drugs alone. This synergistic combination may allow less DOX to be used in TNBC treatment, thus reducing the extreme side effects.



Veratridine functions as a potential anti-mTORC2-Rictor tumorigenic pathway inhibitor in human colorectal cancer

Morgan Eikanger and Khosrow Rezvani

Department of Basic Biomedical Sciences, University of South Dakota, Vermillion, SD

We have shown that veratridine (VTD), a plant alkaloid, can transcriptionally increase UBXLN2A, a tumor suppressor protein, by targeting the overactive mTORC2 tumorigenic pathway in colorectal cancer (CRC). Our recent publication indicates that UBXLN2A targets Rictor, a key member in the mTORC2 protein complex. We hypothesized that VTD-dependent induction of UBXLN2A can inhibit the RICTOR-mTORC2 pathway, which is responsible for tumor growth, migration, and metastasis. Inhibition of this tumorigenic pathway means less angiogenesis and smaller populations of positive colon cancer stem cells. Migration experiments in living cells and biomechanical assays in 3D collagen revealed that VTD successfully reduces cell migration and the cells' ability to generate force and stiffen the matrix. Vehicle and VTD-treated C57BL mice with progressing tumor masses in the colon and rectum revealed that IP injection of VTD (0.1 mg/kg) could significantly decrease tumor growth. These findings provide an attractive and promising target for the next generation of drugs capable of targeting metastatic CRC.

Targeted Combination Therapy for Pancreatic Cancer Management

Paras Giri, Ashish Kumar, Sathish Venkatachalam, Buddhadev Layek

Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

Pancreatic cancer is the 3rd leading cause of cancer-related death in the USA with a 5-year survival rate of 12%. Thus, we developed a tumor-targeted delivery approach of combination therapy for effective management of pancreatic cancer as compared to conventional therapy. Initially, we determined the synergistic potential of the oxaliplatin (OXP)/entinostat (ENT) combination in both mouse (KPC) and human (PANC-1) pancreatic cancer cells. KPC and PANC-1 cells treated with different drug combinations showed synergistic potential at various combination ranges using combenefit software. Furthermore, the synergistic combination was verified via a colony formation assay. Colony numbers were reduced to 73.96%, 75.69%, and 29.34% in ENT, OXP, and combination treatment respectively as compared to control. After that, individual PLGA (Polylactic glycolic acid) nanoparticle containing OXP and ENT was formulated. The in vitro cytotoxicity study revealed that individually encapsulated OXP and ENT showed more significant pancreatic cancer cell inhibition than their solution counterpart.

Synergistic drug combinations to kill triple-negative breast cancer cells

Rayat Hossain, Narendra Kale, Sathish Venkatachalem, Sanku Mallik

Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

Hypoxia in solid tumors is linked to increased invasiveness, difficulty in treatment, and poor patient outcomes. As such, solid triple-negative breast tumors require a targeted drug delivery system that also controls anticancer drug release and reduces harmful side effects. Polymersomes, nanoparticles capable of encapsulating drugs, serve as controllable vehicles for drug delivery. Our initial imaging studies with triple-negative breast cancer cell line MDA-MB-231 demonstrated the overexpression of the receptor SLC7A11 in hypoxic conditions. This receptor promotes tumor survival and is the focus of targeted delivery. This study determined if polymersomes conjugated with sulfasalazine on the outer surface (for targeting) and encapsulating conventional anticancer drug doxorubicin and metformin can achieve synergy and limit doxorubicin concentrations. Future studies would investigate the effectiveness of polymersomes against patient-derived cells and mouse studies.



In-vitro Tumor Mimetic Spheroid Model: Void Space within a Self-detachable Crosslinked Hydrogel

Narendra Kale, Connor Edvall, Chukwuebuka Ozoude, Sanku Mallik

Pharmaceutical Sciences Department, North Dakota State University, Fargo, ND

Three-dimensional (3D) spheroid cell culture models are crucial in screening anticancer drugs in vitro and understanding pancreatic tumor cell behavior. However, the current in-vitro models require highly skilled techniques and often lack reproducible results. We developed an in-vitro, tumor mimetic, self-detachable, cancer cell spheroid model, which provides the confined space of tumor microenvironment, convenient spheroid retrieval, immunostaining, treatment, and imaging. We prepared void space within alginate macrobeads by ionic disintegration and subsequent destabilization with bovine serum albumin to retrieve spheroid cultured inside. Quantitative immunofluorescence image analysis of the cultured BxPC-3 cells (pancreatic cancer) spheroids showed enhanced expressions of the hypoxia-inducible factor-1 α (HIF-1 α) and carbonic anhydrase-9, like monolayer cultures of cancer cells in hypoxia (0.2% oxygen). The present work highlights an in-vitro spheroid model closer to the pancreatic tumor microenvironment with user-friendly cell seeding, spheroid retrieval, and immunostaining steps.

Targeting platelet-cancer crosstalk as a therapeutic strategy for pancreatic cancer

Ying Kang, Emmanuel Boadi Amofo, Philomena Entsie and Elisabetta Liverani

Pharmaceutical Sciences Department, North Dakota State University, Fargo, ND

Pancreatic cancer is one of the most malignant tumors with the highest risk of thrombosis. The current treatments are insufficient; we need new therapies. Pancreatic cancer cells and platelets can communicate during cancer through ADP. Targeting the crosstalk between platelets and pancreatic cancer can provide a new therapy. P2Y₁₂ is an ADP receptor essential for platelets and expressed in pancreatic cancer cells. Whether blocking P2Y₁₂ alters platelet-cancer cell crosstalk is unclear. We treated pancreatic cancer cells (PANC-1 and BxPC-3) with ticagrelor (P2Y₁₂ antagonist) in the presence and absence of platelets and measured platelet aggregation and cancer cell proliferation and migration. Platelet exposure enhanced PANC-1 or PANC-1 migration and growth. Ticagrelor decreased PANC-1 proliferation and migration alone or with platelets. Ticagrelor also decreased cancer cell-induced platelet aggregation. Ticagrelor modulates platelet-cancer crosstalk by targeting both cells.

Modeling Oxaliplatin Resistance in Pancreatic Cancer Cell Lines

Hannah Khan, Katie Reindl

Department of Biological Sciences, North Dakota State University, Fargo, ND

Pancreatic ductal adenocarcinoma (PDAC) is a lethal solid malignancy characterized by a 12% 5-year survival rate. Reasons for this abysmal survival rate include late detection due to obscure symptoms and acquisition of drug resistance. The mechanisms of acquired drug resistance in pancreatic cancer are not fully understood. Therefore, by modeling acquired drug resistance in pancreatic cancer cell lines, further investigation into the mechanisms of drug resistance can occur. One common drug used for pancreatic cancer treatment is the platinum-based drug, oxaliplatin. Three human pancreatic cancer cell lines, PANC-1, MIA PaCa-2, and Capan-2, were treated with oxaliplatin at increasing concentrations, allowing for resistant cell lines to be created. Drug-resistant PDAC cells will be used to identify mechanisms of drug resistance that may include changes in DNA sequence, RNA and protein expression, and DNA repair. Further, the drug-resistant cell lines will be used to investigate additional therapeutic options to enhance cancer cell death.



Finite element approach of analyzing pancreatic cancer patient samples using deterministic lateral displacement.

Sameera Lakshan, Yongki Choi

Department of Physics, North Dakota State University, Fargo, ND

Deterministic lateral displacement (DLD) is a fluid physics-based, microfluidic technique used to separate biomarkers based on their size. It has the potential to sort, isolate, and identify biomarkers from biofluid samples. DLD works by exploiting differences in the way particles move through a series of asymmetric pillars in a microchannel. The DLD method has several advantages over other biomarker separation techniques, including its ability to separate a wide range of biomarker molecule sizes, its high throughput, and its compatibility with a variety of fluids. Here, we investigate trajectories of biomarkers with different sizes in a DLD device using finite element software, COMSOL Multiphysics. By varying the size and dimension of pillars, a set of an array, and multiple arrays in one device, we examine the correlation between fluid dynamics, size-dependent particle separation, and particle-pillar interactions, and how this relationship impacts the path of the particle trajectories.

Enedione derivatives as a potential cancer treatment through the inhibition of COPZ1

Allana C. F. Martins (1), Barbara Mitsuyasu Barbosa (2), Ingridhy Ostaciana Maia Freitas da Silveira (1), Roberto da Silva Gomes (1)

(1) Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

(2) Department of Chemical and Biological Sciences, Institute of Biosciences, Sao Paulo State University (UNESP), Botucatu, SP, Brazil

Cancer is a leading cause of death worldwide. COPZ1 and its paralogous COPZ2 were identified as essential for cell survival. Both COPZ1 and COPZ2 are expressed in almost the same level in normal cells. Interestingly, in tumor cells, COPZ2 is downregulated. This suggests that the COPZ1 knockdown may suppress tumor growth selectively. In this work, molecular docking, synthesis, and cell biology were performed. A set of 84 molecules were submitted to molecular docking, and 4 compounds containing the active metabolite 4-aminoantipyrine and enedione fragment were selected for synthesis and in vitro evaluation. Also, RT qPCR confirmed that the two isoforms COPZ1 and COPZ2 are expressed at similar levels in normal cells, while COPZ2 is downregulated in tumor cell lines. Interestingly, the selected 1-4 compounds showed cellular growth inhibition of MIA PaCa-2 and AsPC-1 cell lines, but not for normal cell line. The tested compounds can target COPZ1-dependent tumor cells; therefore, they are great candidates for further studies aiming to develop a selective treatment for cancer.

Integrin $\alpha 5 \beta 1$ promotes vitronectin and fibronectin expression in pancreatic cancer.

Md Saimon Mia and Sijo Mathew

Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

Extracellular matrix proteins present in the tumor microenvironment significantly contribute to the development of desmoplasia in PDAC. Integrins present on the cell surface mediate the bidirectional communications between tumor cells and their desmoplastic microenvironment. Genome analysis indicated that the upregulation of integrin subunits is correlated with patient survival in PDAC. Therapeutic inhibition with small molecules or antibodies against integrin was developed to treat cancers as they are involved in many of the tumor-promoting cellular functions. Using cell models, this study tested the hypothesis that the upregulation of integrin $\alpha 5 \beta 1$ promotes desmoplasia in PDAC microenvironment. Integrin $\alpha 5 \beta 1$ knockdown/deletion significantly decreased the expression integrin $\alpha 5 \beta 1$. A significant decrease in fibronectin and vitronectin expression was observed in integrin $\alpha 5 \beta 1$ downregulated cells. This also correlated with lower cell adhesion and migration. These results suggest integrin $\alpha 5 \beta 1$ promotes the tumor microenvironment modification in PDAC and contribute to poor patient survival.



Animal Core Facility

Jiyan Mohammad, Ph.D.

Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

The North Dakota State University Center for Diagnostic and Therapeutic Strategies in Pancreatic Cancer (CDTSPC) maintains a variety of resources to support researchers at NDSU. The animal core facility is one of the resources at NDSU for conducting in vivo studies. One of the roles of the animal core facility is to coordinate access to state-of-art methods to study the efficacy and toxicity of new therapeutic agents using models that are standard in the field. The other role is to help Junior investigators to conduct independent preclinical studies by providing expertise in in vivo studies; including experimental design, protocol development, training researchers, and study initiation. Our capabilities include both subcutaneous and orthotopic tumor implantations, spontaneous tumor development (genetically engineered mouse) models, and animal dosing by all common routes of administration, e.g. intraperitoneal, intravenous, oral and subcutaneous, and in combination. These resources will enable NDSU researchers and collaborating scientists to strengthen and sustain biomedical research programs and as result acquire external funds.

Effect of pericyte re-modeling in PDAC tumor progression and metastasis.

Vikneshwari Natarajan, Sangdeuk Ha, and Jiha Kim

Cellular and Molecular Biology, Department of Biological Sciences, North Dakota State University, Fargo, ND.
Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

Pancreatic ductal adenocarcinoma (PDAC) tumor microenvironment harbors morphologically aberrant leaky vessels contributing to hypoxia and impaired immune response, likely reducing the efficacy of cancer therapies. Pericyte coverage significantly correlates with vascular integrity/function, and our previous study showed that abundant aSMA-expressing pericytes in PDAC are associated with non-functional tumor vasculature. As an attempt to deplete these pathological pericytes, we used a GEMM, which allows us to ablate PDGFRB⁺ pericytes upon Ganciclovir treatment. Since most aSMA⁺ pericytes are also PDGFRB⁺, this model system systemically removed pathological pericytes aSMA⁺/PDGFRB⁺ in PDAC tumors. However, despite the decrease in overall tumor size, the remaining vessels were leakier, structurally unstable, and, importantly, expressed aSMA. This study suggests that physically removing the pericytes is not the best way of addressing the pathological phenotype. Instead, there is a need to develop innovative ways to re-functionalize abnormal vessels by re-investing into healthy pericytes.

Synergistic anticancer effects of two drug combinations on pancreatic ductal adenocarcinoma cell lines

Chukwuebuka Ozoude, Narendra Kale, Sanku Mallik

Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND

Pancreatic ductal adenocarcinoma is a fatal disease with a poor prognosis, necessitating the urgent need to develop new therapeutic strategies. Hypoxia is a significant characteristic of solid tumors. Hypoxia increases pancreatic cancer progression, metastasis, and reduces the effectiveness of chemotherapy. We encapsulated an anticancer drug (gemcitabine) and a CXCR4 receptor antagonist (plerixafor) in bilayer vesicles (polymersomes) prepared from amphiphilic block copolymers. Synergy studies were conducted to determine the combinations of plerixafor and gemcitabine using the CombenefitTM software. The synergistic combination of gemcitabine and plerixafor showed increased potency in hypoxia compared to normoxia.



Anterior Gradient 2 (AGR2) knockdown increases endoplasmic reticulum proteotoxic stress in PDAC cells

Philip Salu and Katie Reindl

Department of Biological Sciences, North Dakota State University, Fargo, ND

Anterior Gradient 2 (AGR2) is a proto-oncogene involved in the tumorigenesis of many cancers, including pancreatic ductal adenocarcinoma (PDAC). AGR2 is localized in the endoplasmic reticulum, where it is involved in protein-disulfide isomerase reactions to ensure proper folding, thereby preventing proteotoxic stress resulting from the very high transcriptional output by cancer cells.

Mechanistic studies of UBXN2A-RICTOR-mTORC2 axis in human colorectal cancer

Sanam Sane (1), Rekha Srinivasan (1), Rashaun A. Potts (1), Morgan Eikanger (1), Jessica Freeling (1), Ryan M. Antony (1), Douglas Lynch (2), Jonathan Bleeker (3), Hassan Turaihi (4), Angela Pillatzk (5), Khosrow Rezvani (1)

(1) Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota, 414 E. Clark Street, Lee Medical Building, Vermillion, SD, USA.

(2) Laboratory Medicine and Pathology, Sanford School of Medicine, Sioux Falls, SD, USA.

(3) Sanford Cancer Center, Sioux Falls, SD, USA.

(4) Sanford Surgical Associates, Sioux Falls, SD, USA.

(5) Veterinary and Biomedical Sciences Department, Animal Disease Research and Diagnostic Laboratory, South Dakota State University, Brookings, SD, USA.

There is a clear need to develop more effective targeted therapies to decrease the high mortality associated with metastatic colorectal cancer (CRC). Recent evidence points to inhibiting a signaling pathway regulated by the mTORC2 complex as a promising approach for effective targeted therapy in CRC. Suppression of mTORC2 signaling inhibits CRC cell proliferation and sensitizes CRC cells to standard-of-care therapies. The Rictor protein is a critical component of the mTORC2 complex that increases CRC and drives aberrant mTORC2 and AKT signaling in CRC cells. The current study leverages evidence that the downregulation of Rictor may be a promising approach for targeting mTORC2 signaling for therapeutic benefit in CRC patients. We found a tumor-suppressive ubiquitin-like protein, UBXN2A, induces degradation of Rictor in CRC cells, inhibiting downstream Rictor-mTORC2-regulated cancer-associated processes such as cell growth, survival, and migration. UBXN2A induction in patient tumor-derived organoids suppresses the mTORC2 pathway. These findings provide new insights into the potent anti-cancer function of a Ubiquitin-like protein in patients with CRC.

Nanomechanics of membrane receptor-ligand adhesion

Sakurako Tani, Yongki Choi

Department of Physics, North Dakota State University, Fargo, ND

The cellular membrane and receptors play important roles in various cellular functions, such as signaling, communication, adhesion, and disease development. For example, cancer cells activate particular signals to regulate the deformability of the cytoskeleton structure during EMT for tumor invasion, progression, and metastatic expansion. These cells also elevate the expression of the receptors for amplifying cell-to-cell signaling and cell-to-ECM adhesion. Using the single-molecule force spectroscopy method, we have begun to identify the dynamics of membrane structure and the regulation of receptor's interactions with the ligands, as well as evaluate the feasibility of distinguishing and manipulating receptor-ligand interactions. Additionally, our data demonstrate that the force probing on the membrane surface can detect short-lived receptor movements, focal adhesion of receptors, and multivalent interactions of receptor-ligand interactions. These results provide new knowledge about receptor-ligand binding dynamics and multivalent binding selectivity, affinity, and stability, which is key information to design novel and effective receptor-based nanoparticles for cell imaging, drug delivery, and chemotherapeutics.

NDSU does not discriminate in its programs and activities on the basis of age, color, gender expression/identity, genetic information, marital status, national origin, participation in lawful off-campus activity, physical or mental disability, pregnancy, public assistance status, race, religion, sex, sexual orientation, spousal relationship to current employee, or veteran status, as applicable.

Direct inquiries to Vice Provost, Title IX/ADA Coordinator, Old Main 201,
(701) 231-7708, ndsu.eoaa@ndsu.edu.