Nanotechnology-based sensor developed to measure microRNAs in blood, speed cancer detection

Nov. 17, 2015

INDIANAPOLIS -- A simple, ultrasensitive microRNA sensor developed by researchers from the School of Science at Indiana University-Purdue University Indianapolis, the IU School of Medicine and the IU Melvin and Bren Simon Cancer Center holds promise for the design of new diagnostic strategies and, potentially, for the prognosis and treatment of pancreatic and other cancers.

In a study published in the November issue of ACS Nano, a peer-reviewed journal of the American Chemical Society focusing on nanoscience and nanotechnology research, the IUPUI researchers describe their design of the novel, low-cost, nanotechnology-enabled reusable sensor. They also report on the promising results of tests of the sensor's ability to identify pancreatic cancer or indicate the existence of a benign condition by quantifying changes in levels of microRNA signatures linked to pancreatic cancer. MicroRNAs are small molecules of RNA that regulate how larger RNA molecules lead to protein expression. As such, microRNAs are very important in biology and disease states.

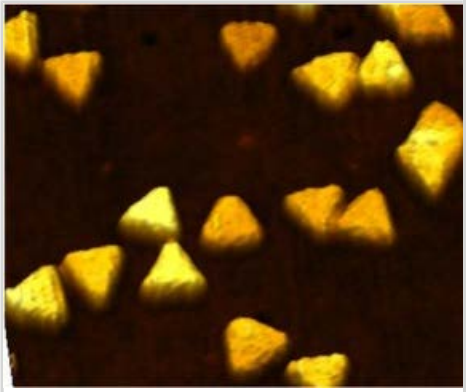
"We used the fundamental concepts of nanotechnology to design the sensor to detect and quantify biomolecules at very low concentrations," said Rajesh Sardar, Ph.D., who developed the sensor. "We have designed an ultrasensitive technique so that we can see minute changes in microRNA concentrations in a patient's blood and confirm the presence of pancreatic cancer." Sardar is an assistant professor of chemistry and chemical biology in the School of Science at IUPUI and leads an interdisciplinary research program focusing on the intersection of analytical chemistry and the nanoscience of metallic nanoparticles.

"If we can establish that there is cancer in the pancreas because the sensor detects high levels of microRNA-10b or one of the other microRNAs associated with that specific cancer, we may be able to treat it sooner," said Murray Korc, M.D., the Myles Brand Professor of Cancer Research at the IU School of Medicine and a researcher at the IU Simon Cancer Center. Korc worked with Sardar to improve the sensor's capabilities and led the testing of the sensor and its clinical uses as well as advancing the understanding of pancreatic cancer biology.

"That's especially significant for pancreatic cancer, because for many patients it is symptom-free for years or even a decade or more, by which time it has spread to other organs, when surgical removal is no longer possible and therapeutic options are limited," said Korc. "For example, diagnosis of pancreatic cancer at an early stage of the disease followed by surgical removal is associated with a 40 percent five-year survival. Diagnosis of metastatic pancreatic cancer, by contrast, is associated with life expectancy that is often only a year or less.

"The beauty of the sensor designed by Dr. Sardar is its ability to accurately detect mild increases in microRNA levels, which could allow for early cancer diagnosis," Korc added.

Over the past decade, studies have shown that microRNAs play important roles in cancer and other



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Media Contacts

Cindy Fox Aisen

Indianapolis

Office 317-843-2276

caisen@iupui.edu

diseases, such as diabetes and cardiovascular disorders. The new IUPUI nanotechnology-based sensor can detect changes in any of these microRNAs.

The sensor is a small glass chip that contains triangular-shaped gold nanoparticles called "nanoprisms." After dipping it in a sample of blood or another body fluid, the scientist measures the change in the nanoprism's optical property to determine the levels of specific microRNAs.

"Using gold nanoprisms may sound expensive, but it isn't because these particles are so very tiny," Sardar said. "It's a rather cheap technique because it uses nanotechnology and needs very little gold. $250 worth of gold makes 4,000 sensors. Four thousand sensors allow you to do at least 4,000 tests. The low cost makes this technique ideal for use anywhere, including in low-resource environments in this country and around the world."

Indiana University Research and Technology Corporation has filed a patent application on Sardar's and Korc's groundbreaking nanotechnology-enabled sensor. The researchers' ultimate goal is to design ultrasensitive and extremely selective low-cost point-of-care diagnostics enabling individual therapeutic approaches to diseases.

Currently, polymerase chain reaction technology is used to determine microRNA signatures, which requires extraction of the microRNA from blood or other biological fluid and reverse transcription or amplification of the microRNA. PCR provides relative values. By contrast, the process developed at IUPUI is simpler, quantitative, more sensitive and highly specific even when two different microRNAs vary in a single position. The study demonstrated that the IUPUI nanotechnology-enabled sensor is as good as if not better than the most advanced PCR in detection and quantification of microRNA.

In addition to Sardar and Korc, authors of "Label-Free Nanoplasmonic-Based Short Noncoding RNA Sensing at Attomolar Concentrations Allows for Quantitative and Highly Specific Assay of MicroRNA-10b in Biological Fluids and Circulating Exosomes" are School of Science at IUPUI graduate students Gayatri K. Joshi, Thakshila Liyanage, and Katie Lawrence; School of Medicine research analyst Samantha Deitz-McElyea (an alumna of the School of Science); and IU undergraduate Sonali Mali.

Sardar and Korc are co-principal investigators on the IUPUI Funding Opportunities for Research Commercialization and Economic Success and IU Collaborative Research Grant funding that supported the study, which was also supported by a U.S. Public Health Service grant (CA-75059) awarded to Korc by the National Cancer Institute.

Changes in brain associated with peripheral nerve issues caused by cancer therapy

Nov. 16, 2015

INDIANAPOLIS -- Researchers at Indiana University School of Medicine have identified physiological changes in the brain that appear to be associated with peripheral nerve-related symptoms caused by chemotherapy.

In research newly reported in the Journal of Clinical Oncology, scientists used magnetic resonance imaging to study changes in brain blood flow and density of gray matter in breast cancer patients receiving chemotherapy, comparing them to participants not undergoing chemotherapy. The study is believed to be the first to identify structural and functional changes in the brain associated with peripheral neuropathy caused by chemotherapy to treat breast cancer.

Chemotherapy-induced peripheral neuropathy is a common side effect of chemotherapy treatments. Patients can experience a broad range of symptoms, including numbness, tingling, pain, muscle weakness, balance problems, and difficulty walking.

The study found that chemotherapy-induced peripheral neuropathy was associated with increased blood flow in areas of the brain that are associated with processing of pain sensations. Both peripheral neuropathy and associated blood flow were associated with gray matter density change, such that individuals with lower gray matter density showed lower blood flow and reported fewer symptoms of peripheral neuropathy.

"Most studies to date have focused on either cognitive or peripheral nerve changes after cancer treatment without examining the possible relationship of both to underlying brain mechanisms," said Andrew Saykin, Psy.D., director of the IU Center for Neuroimaging and Raymond C. Beeler Professor of Radiology. "This analysis connected all of these issues suggesting the need for a more comprehensive approach to neural changes in cancer patients."

Additional studies are needed, including work that would incorporate objective measures of peripheral neuropathy symptoms, but the changes in brain structure and blood flow identified in this study could result in decreased patient perception and reporting of peripheral neuropathy symptoms.

"It is possible that individuals experiencing cognitive changes as a result of chemotherapy may be under-reporting chemotherapy-induced peripheral neuropathy symptoms, which could impact diagnosis and treatment, as well as function in everyday life," said Kelly N.H. Nudelman, Ph.D., post-doctoral fellow in radiology and imaging sciences at the IU School of Medicine.

In addition to Dr. Nudelman, first author, and Dr. Saykin, researchers contributing to this study were Brenna C. McDonald, Dori J. Smith, John D. West, Darren P. O'Neill and Bryan P. Schneider of the IU School of Medicine, Noah R. Zanville and Victoria L. Champion of the IU School of Nursing, and Yang Wang of the Medical College of Wisconsin.

IU Neuroscience Research Building

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Media Contacts

Eric Schoch

Indianapolis

Office 317-274-8205

eschoch@iu.edu

The research was supported by grants from the National Cancer Institute (R01 CA101318, R01 CA082709, and R25 CA117865), the National Institute on Aging (R01 AG19771 and P30 AG10133), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U54 HD062484) of the National Institutes of Health; the Indiana Clinical and Translational Sciences Institute (UL1 RR025761, RR027710-01, and RR020128) and an Indiana University Melvin and Bren Simon Cancer Center American Cancer Society institutional grant.

IUSCC news

November 2015

News briefs

Bioinformatics core open

The Collaborative Core for Cancer Bioinformatics (C3B) is now open for bioinformatics service and consultation to both Indiana University Melvin and Bren Simon Cancer Center (IUSCC) and Purdue University Center for Cancer Research (PUCCR) members. Supported by the Walther Cancer Foundation, C3B aims to integrate and accelerate cancer discovery, drug discovery, and precision medicine through joint bioinformatics, molecular genetics, and genomics research. Cancer investigators can submit their projects through the C3B Website. C3B is a shared core facility, which is managed by two dedicated PhD bioinformaticians to serve both IU and Purdue cancer center members.

IU cancer researcher receives $450,000 Komen research grant

An Indiana University cancer researcher has been awarded a $450,000 research grant from Susan G. Komen to identify epigenetic markers that drive breast cancer development.
full story>

Reminders

Core update

The Bio-Plex Core is now known as the Multiplex Analysis Core.

Christie Orschell, PhD, the core's director, explained that the core no longer houses only the BioPlex instrument, thus, the name change. We now also have the Aushon, another type of multiplex immunoassay platform, that can quantitate protein to the femtogram level," Dr. Orschell said.

She added: "We offer multiplex immunoassay-based technologies for quantitation of proteins and other analytes from a wide range of tissue types and large number of species."

The core is located in Walther Hall, Room 335.

Learn more.

New IU Simon Cancer Center PowerPoint template available

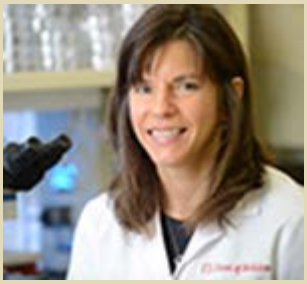
Are you about to put together a PowerPoint presentation in which you'll be representing the IU Simon Cancer Center? If so, we invite you to use the newest

cancer center template:
http://cancer.iu.edu/documents/IUSCC_PowerPoint_Template_2015.pptx.

You'll find a title page and two options for subsequent pages: One page with the IU Simon Cancer Center signature (logo), and a page without the signature. This gives you the option of either using the signature on every page or using it more sparingly, either throughout the presentation, or perhaps only for the final slide.

The new template adds consistency to the IU Simon Cancer Center's overall look. The template's design takes elements from the Website (www.cancer.iu.edu), the monthly e-letter, and internal announcements.

Cancer center members in the news



Orschell

As previously reported, **Christie Orschell**, PhD, and colleagues performed preclinical work that contributed to the approval of Neupogen (filgrastim) to treat adult and pediatric patients exposed to myelosuppressive doses of radiation. Such exposure may happen in a radiation nuclear event. More recently, the FDA approved Neulasta, the long-acting form of Neupogen, for the treatment of acute radiation syndrome (ARS). Dr. Orschell's lab contributed by testing ARS in mouse models as well as testing in a pediatric mouse model of ARS to understand how to use the drug in the pediatric population.

Effective Dec. 1, **Thomas Hurley**, PhD, associate chair and professor of the Department of Biochemistry and Molecular Biology, will serve as interim chair of the department. The appointment is prompted by the departure of **Zhong-Yin Zhang**, PhD, chair and Robert A. Harris professor. Dr. Zhang will join Purdue University, where he received his PhD in biochemistry, as head of the Department of Medicinal Chemistry and Molecular Pharmacology, effective Jan. 4.

Paul Haut, MD, associate professor of pediatrics at IU School of Medicine and interim president and chief medical officer, Riley Hospital for Children at Indiana University Health, has been appointed to the Graduate Medical Education Board by Gov. Mike Pence. The board oversees the expansion of medical education in Indiana through the funding of new residency program slots at licensed hospitals.

Mark Kelley, PhD, received the inaugural Innovation to Enterprise Research Commercialization Award during the recent IUPUI Innovation Forum and Showcase. He received the award for his groundbreaking work that helped ApeX Therapeutics -- a company he founded in 2005 -- develop a protein signaling inhibitor known as APX3330 that has shown "dramatic" efficacy against pre-clinical models of pancreatic cancer. This includes a two- to threefold reduction in tumors and less metastasis. Human clinical studies into APX3330's effectiveness are expected to begin soon.

The following cancer center members are scheduled to attend the San Antonio Breast Cancer Symposium in December: **Anna Maria Storniolo**, MD; **Kathy Miller**, MD; **Sunil Badve**, MBBS, MD; **Hari Nakshatri**, PhD; **Lida Mina**, MD; **Bryan Schneider**, MD; and **Milan Radovich**, PhD.

Costantine Albany MD, has been awarded a 2015 Clinical Scholar Award from the Alliance for Clinical Trials in Oncology for the scientific merit and feasibility of his proposed research into cisplatin-induced peripheral neuropathy.

Albany

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