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## WHAT'S INSIDE

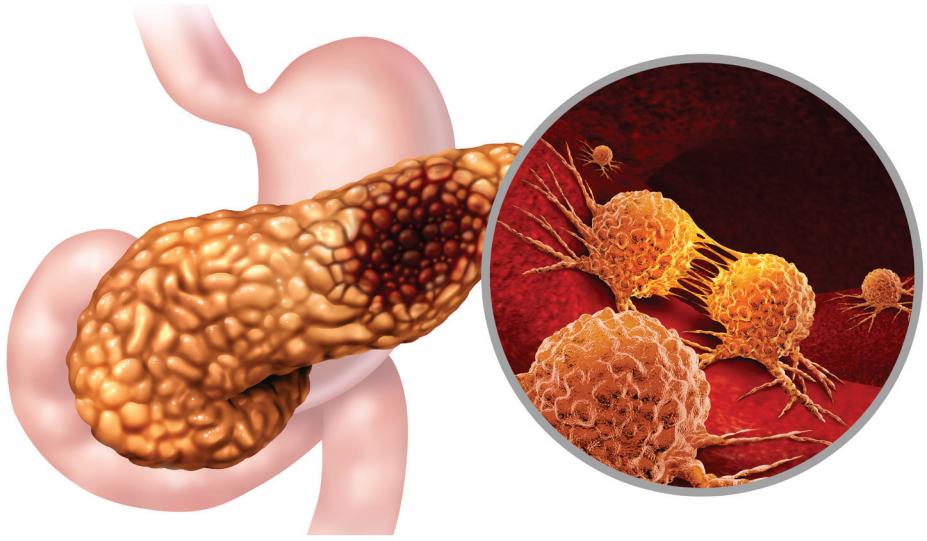


# Answering questions about APA

## Researchers shine light on how regulatory mechanism impacts pancreatic cancer

**BY KELSEY KAUSTINEN**

BUFFALO, N.Y.—Pinpointing culprits that aid in the progression of cancer, such as oncogenes or easily hijacked immune checkpoints, improves our understanding of the disease and provides new targets for combating it. One such culprit, a gene regulatory mechanism known as alternative polyadenylation, was recently subjected to its first large-scale analysis in a single cancer type by Roswell Park Comprehensive Cancer Center researchers, who discovered that it plays a key role in the development of pancreatic cancer.



**According to Roswell Park researchers, a gene regulatory mechanism known as alternative polyadenylation, or APA, plays a key role in the development of pancreatic cancer.**

Dr. Michael Feigin, an assistant professor of oncology in the Department of Pharmacology and Therapeutics, led this work, along with postdoctoral fellow Dr. Swati Venkat and colleagues. Their results were published in *Genome Research* in an article titled "Alternative polyadenylation drives oncogenic gene expression in pancreatic ductal adenocarcinoma." This research was funded in part by grants from the National Cancer Institute and the U.S. Department of Defense, as well as donations to Roswell Park.

Alternative polyadenylation regulates the expression of genes in cells—including oncogenes, genes known to drive cancer. As the authors of the *Genome Research* paper explain, "Alternative polyadenylation (APA) is a gene regulatory process that dictates mRNA 3' UTR length, resulting in changes in mRNA stability and localization. APA is

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# Under the umbrella

## *Cytel touts basket and umbrella trial design*

**BY MEL J. YEATES**

WALTHAM, Mass.—A new paper authored by statistical experts at Cytel Inc. has been published in *CA: A Cancer Journal for Clinicians*. Cytel hopes that the paper, entitled "An Overview of Precision Oncology Basket and Umbrella Trials for Clinicians," will be a valuable resource for increasing master protocol trial literacy among the many clinicians and researchers who may not be familiar with these types of trials.

*DDNews* spoke with several Cytel spokespersons: Ed Mills, vice president of real-world evidence; Jay Park, director; Kristian Thorlund, vice president of real-world analytics; Grace Hsu, a senior statistician; and Ellie Siden, a former research associate.

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**"Given that these trials tend to be of a larger scale, it will be difficult for individual companies—especially for small biotechs—to undertake them without collaboration," note Cytel researchers of umbrella and basket trials. Among the authors of a recent paper on such trials was Jay Park, pictured here.**

According to the researchers, "Basket and umbrella trials are two types of master protocols, also commonly referred to as complex innovative trial designs (CIDs). Master protocols generally refer to a single overarching protocol developed to evaluate multiple hypotheses with the general goal of improving efficiency and uniformity through standardized procedures. These trials have been motivated by advancements in 'omics' technologies and improvements in biomarker research, particularly in oncology, that allow us to better understand how cancers work and how we could potentially treat them."

"In contrast to conventional clinical trials, 'basket trials' aim to identify therapies that are agnostic to tumor or histology (*i.e.* tumor-agnostic therapies) by testing them on multiple diseases that have common

**CYTEL** CONTINUED ON PAGE 30

# Digging into diabetes

## Researchers are gaining new insights into the mechanisms behind diabetes

**BY MEL J. YEATES**

JUPITER, Fla. & NEW YORK—With insulin prices skyrocketing into the proverbial heavens, people with diabetes are no doubt eager to find new therapies that could possibly improve their lives. Now, researchers at both Scripps Research and Mount Sinai have shared news of recent work that could move the industry one step closer to such therapies.

Scientists at Scripps Research have found a new biological mechanism of insulin signaling. Their study, involving the roundworm *C. elegans*, revealed that a "decoy" receptor is binding to insulin molecules and preventing them from signaling for increased insulin production.

"This truncated, 'decoy' receptor that we've found adds yet another layer of complexity to our understanding of insulin signaling," said lead author Dr. Matthew Gill, an associate professor in the department of Molecular Medicine at Scripps Research in Florida.

The research appears in the journal *eLife* and reveals a part of the insulin signaling system that may offer insights into the cellular insulin resistance associated with type

**In recent diabetes research news, scientists at Scripps Research have discovered a new mechanism of insulin signaling, while researchers at Mount Sinai work on a way to induce human beta cell regeneration.**

2 diabetes. The researchers are now assessing whether a similar decoy receptor exists in humans. If so, it could present a new target for research.

Since the 1990s, researchers have recognized that insulin signaling is also an

**DIABETES** CONTINUED ON PAGE 15

# COMMENTARY: THE IMPORTANCE OF THE PHARMACEUTICAL COMPOSITION ANALYZER

*An accurate analyzer can provide simultaneous analysis of entire composition of samples for precision and security*

**BY DEL WILLIAMS ON BEHALF OF KETT US**

FEW INDUSTRIES REQUIRE as much care for precision and security as the pharmaceutical industry. Every part of production and each end result must be made with the utmost accuracy and attention to detail. As measurement requirements become more precise, exceptional accuracy becomes critical, because too much or too little of a substance can significantly affect the potency, effectiveness and overall safety of a drug.

Under the FDA, United States Pharmacopeia (USP) and Pharmaceutical Microbiology Manual (PMM), pharmaceuticals are required to meet strict health and safety regulations when it comes to toxicity, sterility and shelf life.

While pharmaceutical science is an increasingly exact industry and the shelf-life of many products is closely monitored, impurities in a drug can have disastrous effects. As pharmaceuticals are developed, transported and stored for an indeterminate amount of time, at any stage from manufacturer to the consumer these substances and products may develop impurities that make them unsafe for use.

Consequently, pharmaceuticals must be tested for impurities and changes in potency at each step to ensure that they continue to be safe for consumers. Such testing can provide pharmaceutical companies the security of knowing that their products are continuously monitored for precision, correct composition, safety and compliance.

However, conducting frequent compositional analysis tests throughout the process or in the field has traditionally been difficult. In many cases, the primary barrier has been the expertise and time required to conduct such tests. Multiple sophisticated measurement devices, such as for moisture measurement and other elements of composition analysis, had to be operated by trained personnel who could properly calibrate the equipment. Many such tests also required meticulous sample preparation and disposal.

Fortunately, a full range of composition analyzers from handheld to desktop and inline are now available that can help to ensure that each product—every tablet or capsule—is safe to use and will work as intended.

"While composition analyzers are not new to the industry, and their introduction helped to build momentum for the Process Analytical Technology (PAT) movement a decade ago, advanced units today allow even less-skilled personnel to take instant lab-quality tests," says John Bogart, managing director of Kett US, a manufacturer of a full range of organic composition analyzers.

With a single fast, nondestructive test, a composition analyzer can now furnish analysis of a sample's whole composition at once. Such "point-and-measure" options enable multiple readings to be quickly taken at any stage of the process, as well as at loading docks, on trucks, at suppliers or in bins, vats or vessels.

Whether dealing in bulk, dose, tablets, capsules, gel or liquid-based products, by simplifying the process, pharmaceutical manufacturers can increase the quality of their products from chemical receipt, formulation and processing to end product manufacturing and distribution.

## The many benefits of compositional analysis

In pharmaceutical manufacturing, determining a wide variety of compositional characteristics—such as the level of moisture, purity or contaminants in raw inputs, in-process substances and end products—can be essential to ensuring safety and compliance.

Typically, pharmaceuticals require three primary tests, including one that involves moisture. One test determines solid content for quality and for dosage quantification. Another test measures residual solvents, which are sometimes used in the chemistry of production; these need to be below a certain level to be "acceptable" for human consumption. A third test relates to blend homogeneity. When blending solids in a stream, it is necessary to ensure that the blend is sufficiently homogenous, so it is ready to move to the next processing step.

Composition meters can efficiently perform all three of these measurements in a single test. Full-spectrum units can perform not only these three analyses, but also a vital test measuring active pharmaceutical ingredients (APIs).

As such, frequent compositional analysis can help pharmaceutical products stay compliant when sold based on regulated moisture content. Moisture content is measured to get the solids content, and measuring the amount of solid in the dose is required to ensure that the patient receives the correct amount of API. It is also necessary to measure the level of purity/contaminants and other factors that can affect safety and product effectiveness. Prescribed percentages must be met in order to satisfy certain specifications, or the product/substance will not be accepted by the regulating agency.

## Simplifying compositional analysis

Although traditional laboratory and online-based moisture measurement techniques are useful in the right settings, they have lacked the simplicity and flexibility required for frequent spot checks.

One common test is a Karl Fischer test. This procedure calls for chemical reagents to be added to the sample to separate the water from the remaining product. The water removed is then compared with the initial mass or volume. Samples are generally small, making the assumption that a large batch is homogenous. Also, since the chemical reagents need to be used, skilled personnel are required to determine the initial parameters, confirm that the system is properly calibrated and maintained and, at times, required to actually conduct the tests. Disposal of the reagents and waste can be subject to substantial documentation and costly handling.

Another test used is "loss on drying," which measures the total material weight change after drying. However, such tests typically require a sample to be prepared and brought back to the lab. The test takes at least 15 minutes to several hours to perform, which is too slow when more immediate measurements are required. It also requires the sample to be altered or destroyed.

Beyond this, there could be a number of additional primary tests required to determine other necessary characteristics, such as the level of purity or contaminants in a pharmaceutical substance or product. Each of these tests usually requires separate tools, procedures and sample preparation. This requires not only skilled personnel but also extra time and labor for each separate measurement, as well as the additional use of potentially very expensive product which is destroyed in these other tests.

As a result, secondary test methods have typically been used to deliver faster results. This type of test uses an indirect method and a single conversion to achieve accurate results. Secondary measurement techniques are routinely accepted as equal to the gold standard method. Examples are speedometers, common infrared and liquid thermometers, and most pressure gauges. If there is a disadvantage, it is that the instrument must first be calibrated to ensure accurate results. In some cases, calibration could only be performed by trained staff familiar with the equipment.

In response, industry innovators have developed a simplified approach that allows even less-trained personnel to take portable, desktop or in-line, instant composition analysis readings of pharmaceutical industry feedstock, in-process formulations or end products as needed.

The approach involves devices that utilize near-infrared (NIR) light, a highly accurate, non-contact, secondary measurement method that can deliver immediate, laboratory quality composition analysis readings.

"NIR composition analyzers allow very accurate, instant, simultaneous measurement of multiple organic components in solids and liquids without contact or sample preparation, so there is no product contamination when using handheld and inline/online models," says Bogart.

In addition, because the process is non-destructive, samples remain unaltered so they can be used for additional tests or put back into the product stream. Because no direct contact or sample alteration is required, particle size variation and unusual textures are not an issue. This can be important when used with a range of chemicals, formulations, or end products in different settings.

According to Bogart, once a composition analyzer has been calibrated against lab or production standards for the components to be measured (moisture, purity, etc.), the calibrations can be good for the life of the instrument. This is true as the instrument can be continuously verified against stored optical standards that provide full traceability to the original measurement method, and the calibrations are stored in different "channels" in the instrument.

"With a composition analyzer, a NIR light source is reflected off, or transmitted through the liquid or solid sample," says Bogart. "Several organic components can be measured in single test when the light resonates with certain molecules and the analyzer measures the sample's light absorbance values, its 'optical fingerprint.' This is combined with the calibrations stored in different analyzer 'channels' to instantly display multiple simultaneous."

This means that when the sample's compositional accuracy is being tested anywhere within the production process, from manufacturing to distributing, a composition analyzer is able to provide fast information for verification or validation of "release specs."

Because accurate measurement is achieved without pre-processing the samples or waiting for lab results, this dramatically reduces the test cycle, enabling pharmaceutical manufacturers to focus on improving product quality and not on sampling and prep work.

"The goal is for any staff member to be able to successfully use a composition analyzer whenever and wherever it is needed, with minimal required training," says Bogart. "This allows the pharmaceutical industry to be certain that products are of the highest quality."

"The key is to cost-effectively be able to conduct as much testing as required, with full confidence in the results, each and every time," adds Bogart. ■

Del Williams is a technical writer based in Torrance, Calif., who writes about health, business, technology and educational issues. Kett US is a company with a focus on moisture and organic composition analysis, among other related technologies.

## METRICS

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cost across multiple 'omics studies at once. Good samples are a costly overhead expense, rarely done right or in enough numbers. It's harder to fund translational work for proteomics and metabolomics with their dependence on drugs, diet, time of day and lifestyles.

Until we do validate, the markers won't mark. Commercial firms have little incentive to do the work. Monetizing success is much less feasible than for a drug, yet the searching is no less difficult. If the system will not fund clinical validation, there is little point in funding more biomarker discovery. If it is not translated, it's not discovered. Perhaps the Chinese ministries are thinking fewer and better papers, no matter where they are published. We all could benefit. ■

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