



Esther John, PhD,
MSPH, Breast Cancer
Epidemiologist

5



Stanford's
Cell Sciences
Imaging Facility

6

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A P U B L I C A T I O N F O R F R I E N D S O F T H E S T A N F O R D C A N C E R I N S T I T U T E

Steven Artandi, MD, PhD, Named New Director of the Stanford Cancer Institute

He Succeeds Outgoing Director Beverly Mitchell, MD

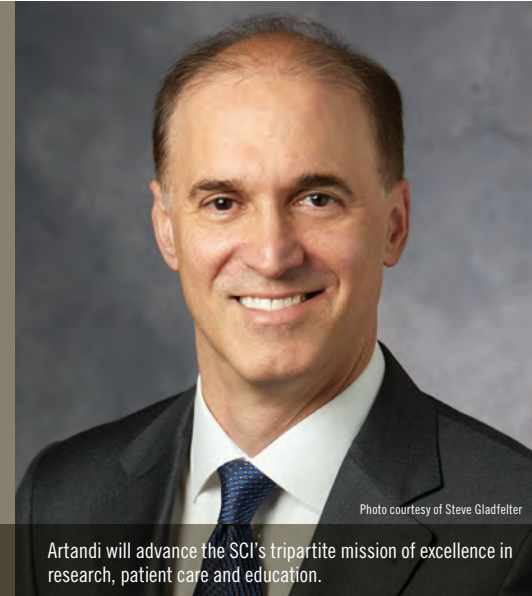


Photo courtesy of Steve Gladfelter

Artandi will advance the SCI's tripartite mission of excellence in research, patient care and education.

FALL 2018

By Krista Conger

Steven Artandi, MD, PhD, professor of medicine and of biochemistry at the School of Medicine, has been named the new Laurie Kraus Lacob Director of the Stanford Cancer Institute, effective October 1, 2018.

Artandi replaces Beverly Mitchell, MD, who has served as director for the past 10 years. Mitchell, a professor of medicine, will continue her involvement with the institute as senior adviser, researcher and mentor.

“A strategic thinker and collaborative physician-scientist, Dr. Artandi’s understanding of the opportunities to develop synergies between the elements of our tripartite mission — excellence in research, patient care

and education — make him uniquely qualified to further the SCI’s goal of translating Stanford discoveries into individualized cancer care,” said Lloyd Minor, MD, dean of the School of Medicine. “His work is already producing new insights into the origins

A medical oncologist and cancer biologist, Artandi studies the role of telomerase in stem cells and cancer.

of cancer, revealing how aspiring cancers circumvent critical bottlenecks encountered during carcinogenesis, and leading to new therapies with the potential to treat many of the most refractory human cancers.”

“I’m very honored to be the next director of the Stanford Cancer Institute, particularly at this exciting juncture in the history of cancer research and cancer therapy,” Artandi said. “We are entering a period during which major translational discoveries will transform our approach to treating cancer patients. Stanford has remarkable strengths in innovation, basic science, clinical medicine and translation. We’re also fortunate to have extraordinary people, including faculty, trainees, nurses and staff. At SCI, we’re uniquely positioned to drive forward the next wave of discoveries to benefit our cancer patients.”

See **NEW DIRECTOR**, page 3

Message from the Director Emeritus

The More We Understand, the More Impact We Can Have



I am very pleased to introduce this fall issue of the SCI News, which contains stories about our initiatives to combat pancreatic cancer and an exciting opportunity to explore the genetic underpinnings of colon cancer funded by the Biden Moonshot initiative. It will also introduce you to the work of two of our wonderful faculty members, Christina Curtis, PhD, MSc, who is exploring the evolution of tumors, and Esther John, PhD, MSPH, a breast cancer epidemiologist.

This will also be the last issue during my tenure as Director of the Stanford Cancer Institute. It has been my privilege to oversee the burgeoning of our cancer programs over the past ten years, ranging from groundbreaking basic science through to the growth of our clinical research initiatives and the development of innovative programs in cancer prevention and population health. These programs were not completely new to Stanford, but our NCI comprehensive designation has increased our emphasis on the integration of research across these disciplines with the goal of improving the prevention, treatment and outcomes of cancer diagnoses. The opportunities at the Stanford Cancer Institute to carry this mission forward are tremendous. The growth and excellence of our clinical programs will allow us to expand our efforts even further toward developing new and more specific therapies and interventions, while we continue to focus on new strategies to understand tumor biology and the behavioral, genetic and environmental risk factors that lead to cancer. We are particularly excited to extend these efforts to our community with an emphasis on underserved patient populations who need better access to cancer care.

It is indeed a great pleasure to welcome Steven Artandi, MD, PhD, as my successor. As you will read in this issue, Steve is a phenomenal scientist who is strongly motivated to lead the SCI into an exciting future. In conclusion, I want to thank all of the readership of SCI News for its strong support of our mission. Cancer presents many complexities and challenges, not only locally but increasingly throughout the world. The more we understand, the more impact we can have. The Stanford Cancer Institute is a place to help make this happen. ■

Beverly S. Mitchell, MD

Director Emeritus and Senior Advisor

The Stanford Cancer Institute

The Stanford Cancer Institute (SCI) provides support and coordination for the range of cancer-related activities occurring at Stanford University, Stanford Health Care, and the Lucile Packard Children's Hospital. Our nearly 500 faculty members belong to more than 30 academic departments from four schools, and represent the wide array of disciplines involved with comprehensive cancer research, treatment, prevention, education, and outreach.

The SCI is a National Cancer Institute-designated Comprehensive Cancer Center, with a scientific agenda combining laboratory research, clinical study, translational programs and population science. The SCI also provides patient care, community education, clinical trials, as well as support and training for the next generation of cancer physicians and researchers.

Simply put, all of our members and resources are focused on one goal: to reduce the occurrence and impact of cancer.

Support the Stanford Cancer Institute

Investigators at Stanford are rewriting our understanding of cancer and transforming how we treat cancer patients. Become an integral partner in these important efforts by donating to the Cancer Discovery Fund. By giving to the Stanford Cancer Institute, you will support cutting-edge, interdisciplinary research that brings new diagnostics and new therapies to cancer patients.

Give today at:
discoveryfund.stanford.edu/goto/SCI

For more information please call (650) 497-6410 or email stanfordmedicine@stanford.edu

NEW DIRECTOR, *continued from page 1*

Artandi came to Stanford in 2000 after completing a fellowship in medical oncology at the Dana Farber Cancer Institute and Massachusetts General Hospital. In 2015, he received an Outstanding Investigator Award from the National Cancer Institute. He earned his MD and PhD in microbiology in 1995 from Columbia University.

“Dr. Artandi is a highly accomplished physician-scientist who will take the Stanford Cancer Institute to the next level,” said Mary Hawn, MD, professor and chair of surgery at Stanford. “He has innovative plans to translate science to patients that will markedly impact care.”

Hawn and Thomas Montine, MD, PhD, professor and chair of pathology, co-chaired the search committee for the new director.

“We are delighted to have Dr. Artandi as the next director for the Stanford Cancer Institute,” Montine said. “His leadership will undoubtedly help the institute continue to improve outcomes for patients facing cancer diagnosis and treatment.”

Artandi Conducts Novel Research on the Role of Telomerase

Artandi, who holds the Jerome and Daisy Low Gilbert Professorship, is a medical oncologist and cancer biologist whose research focuses on the role played by the enzyme telomerase in cancer, aging and stem cell biology.

Artandi and his colleagues recently

found that liver stem cells that express high levels of telomerase act in mice to regenerate the organ during normal cellular turnover or tissue damage, according to a study published online in *Nature* in April 2018. Artandi was the senior author of the study and postdoctoral scholar Shengda Lin, PhD, was the lead author.

Understanding the liver’s remarkable capacity for repair and regeneration is a key step in understanding what

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— Thomas Montine, MD, PhD

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happens when the organ ceases to function properly, such as in cases of cirrhosis or liver cancer.

“The liver is a very important source of human disease,” said Artandi. “It’s critical to understand the cellular mechanism by which the liver renews itself. We’ve found that these rare, proliferating cells are spread throughout the organ, and that they are necessary to enable the liver to replace damaged cells. We believe that it is also likely that these cells could give rise to liver cancers when their regulation goes awry.”

Lin and Artandi wondered whether they could use telomerase expression as a marker to identify the subset of cells

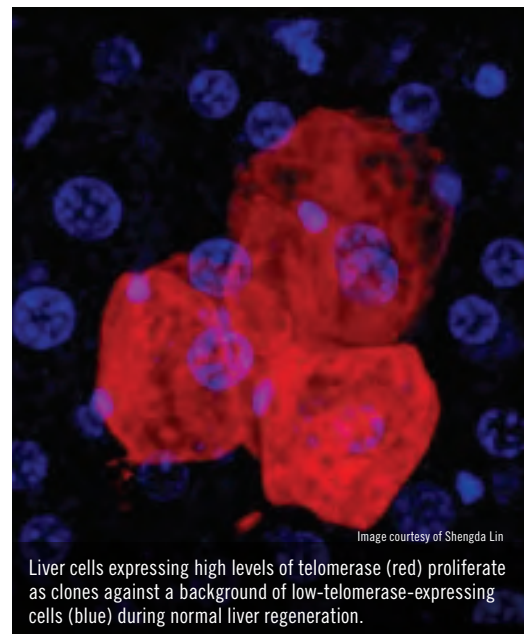


Image courtesy of Shengda Lin
Liver cells expressing high levels of telomerase (red) proliferate as clones against a background of low-telomerase-expressing cells (blue) during normal liver regeneration.

responsible for regenerating the liver during normal turnover. These cells, they believe, could also serve as the cell of origin for liver cancer.

“These rare cells can be activated to divide and form clones throughout the liver,” said Artandi. “As mature hepatocytes die off, these clones replace the liver mass. But they are working in place; they are not being recruited away to other places in the liver. This may explain how the liver can quickly repair damage regardless of where it occurs in the organ.”

“You could imagine developing drugs that protect these telomerase-expressing cells, or ways to use cell therapy approaches to renew livers,” said Artandi.

In addition to his work on liver cells, Artandi’s current research efforts are aimed at understanding the role of pancreatic cancer acinar cells and how they impact the earliest stages of pancreatic cancer development. ■

Pancreas Cancer Research Group Unites Scientists Improving Outcomes in Pancreas Cancer

Research in pancreas cancer is essential to improving outcomes. In spring 2018, a group of Stanford Cancer Institute researchers and clinicians established the Pancreas Cancer Research Group (PCRG), a network of scientists interested in advancing research and care in pancreas cancer. The goal of the PCRG is to facilitate and expedite impactful research on pancreas cancer at Stanford.

“The idea was to bring together people who approach pancreas cancer from different angles, meaning clinicians who treat it, researchers who work on early detection, and basic scientists who do experiments in the laboratory to understand how pancreas cancer develops using mouse models,” said SCI member and PCRG co-leader Laura Attardi, PhD, professor of radiation oncology and of genetics and co-director of the Stanford Cancer Biology Graduate Program. “The goal is to make more progress in this deadly disease by bringing together people who don’t necessarily interact to allow them to brainstorm together.”

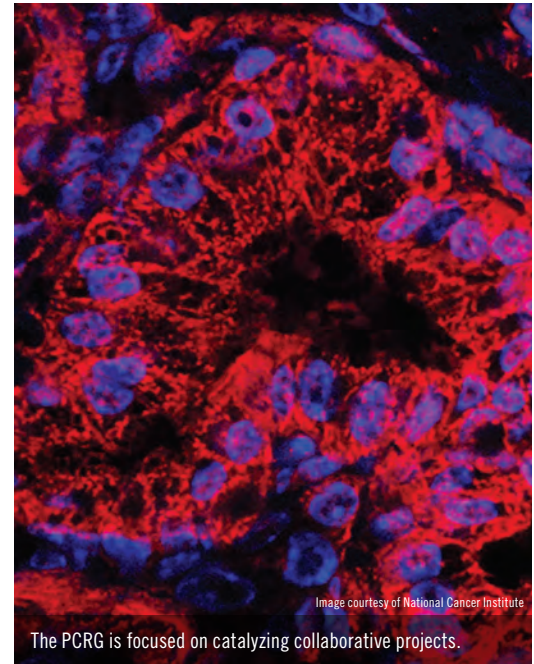
The PCRG is focused on catalyzing collaborative projects through a central website, monthly face-to-face meetings, seed grants, and a program project grant application, according to SCI member and PCRG co-leader George A. Fisher, MD, PhD, professor of medicine (oncology). The group currently encompasses 31 members from various disciplines at Stanford, including pathology, radiology,

gastroenterology, medical oncology, surgical oncology, radiation oncology, genetics, molecular biology, cancer biology, and immunology.

“The group was formulated because we realized there were many different approaches that can be integrated at Stanford,” said SCI member and PCRG co-leader Seung K. Kim, MD, PhD, professor of developmental biology and (by courtesy) of medicine (oncology) and director of the Stanford Diabetes Research Center. “The goals initially are to work better together to develop joint projects, develop more translational applications for basic work, and produce new information for the Stanford community about pancreas cancer.”

To kick off this collaboration, the PCRG held an inaugural retreat in September 2018 where members presented their general research interests and brainstormed ways to join forces through their work. “Great discussions and collaborative projects emerged from these discussions,” Fisher said. “The retreat brought clinical researchers together with laboratory scientists.”

One collaboration has evolved into a program project grant application. The researchers will work on characterizing the immune cell changes that occur when the genetic composition of mice is changed. Research has shown that when P53



The PCRG is focused on catalyzing collaborative projects.

(a critical tumor suppressor) is removed from a mouse pancreas, the mouse rapidly develops pancreas cancer. “We’re trying to understand how the immune cells might change in that setting and whether it gives us an idea of how to develop better immunotherapies,” Attardi explained.

On the clinical side, Stanford is moving toward preoperative chemotherapy rather than surgically removing tumors before patients undergo chemotherapy. The benefit is that it allows clinicians to analyze tumor and blood samples after a tumor is removed to determine the effects of the chemotherapy. With this new method, researchers can evaluate molecular changes in a tumor as a consequence of exposure to new drugs.

Fisher added that the group is committed to supporting clinical and laboratory postdoctoral fellows interested in pancreas-related projects and hopes to have faculty recruitment for a pancreas cancer researcher. ■

Get to Know:

Esther John, PhD, MSPH, Breast Cancer Epidemiologist

Until the 1990s, most large studies on breast cancer included only white women. SCI member Esther John, PhD, MSPH, a cancer epidemiologist who realized the value in studying racial/ethnic minorities, set out to change that. She launched one of the first breast cancer studies to include Latina women, and went on to show just how

different rates of breast cancer are in US-born compared with foreign-born women and how risk factors differ between these groups.



Esther John, PhD, MSPH

“We really don’t understand why the incidence is so different,” says John. “But we do know that what we learn in minority populations can help us with new approaches to cancer as a whole.”

John, now a professor of medicine, came to the SCI in May 2018 from the Cancer Prevention Institute of California. She has co-led the SCI’s Population Sciences Program since 2014 and prior to that the SCI Cancer Epidemiology Program. She says the opportunities for collaboration with clinicians is one of the things that drew her to Stanford.

“Many of my colleagues here are physicians who treat patients, so they can give really valuable clinical

perspective to the work we do as epidemiologists,” she says.

John is continuing to lead and collaborate in a number of ongoing breast cancer studies in her new role at the SCI, including the Breast Cancer Family Registry that has been ongoing since 1995. The registry is based at six study centers around the globe, and John is the PI of the Northern California branch of the registry. She has helped enroll more than 4,000 women with breast cancer from the San Francisco Bay area and their relatives who are at increased risk of breast cancer due to their family history. More than 75% of the Northern California families in the registry are racial/ethnic minorities, who have now been followed for nearly a quarter of a century.

“It’s a very rich resource now, with the amount of data that’s been collected,” says John. “And we’re sharing it with the broader research community at large.”

Despite the advances that have been made in understanding the genetics and molecular underpinnings of breast cancer in the past decades, John says there is still a lot to learn from an epidemiological perspective. Increasingly, studies are focused not on breast cancer as a whole, but on the differences between subtypes of the cancer.

“Not all breast cancer is the same,” says John. “Each molecular subtype has different risk factor profiles and the

incidence of the subtypes also differs between different racial/ethnic groups.”

There are also remaining questions about when in life diet, other lifestyle factors and environmental exposures have the greatest impact on breast cancer risk. Some evidence suggests that exposures in early life could play an important role— John is pursuing this idea as part of the LEGACY Girls Study, another multicenter cohort. Since 2011, girls aged 6 through 13 have been enrolled at 5 sites in the US and Canada. Researchers including John are studying the link between environmental factors and puberty. Earlier puberty has been linked to a heightened risk of breast cancer, so they are curious what can predict earlier puberty.

“If it’s true that early life exposures and lifestyle factors play a role, that gives us new opportunities for prevention in this young population,” says John.

In her new role at Stanford, as she makes inroads into understanding new risk factors for breast cancer, John also hopes her findings can reach the public in a transparent and useful way. Many women, she says, still are not aware of breast cancer risk factors that epidemiologists view as well-accepted, such as daily alcohol consumption or obesity in postmenopausal women.

“There needs to be better communication between scientists and the public,” she says. ■

How Do You See the Inner Working of a Cancer Cell? Stanford's Cell Sciences Imaging Facility

Inside a tumor, molecules zip from place to place, and cluster in unusual areas, helping cancer cells multiply at a speedy pace. To stop tumors from growing, scientists often must aim to put the brakes on these molecules. Doing so requires visualizing the molecules and cells in the first place. Luckily for cancer researchers, modern microscopy has lots to offer them.

“It’s a very exciting time in imaging,” says Jon Mulholland, Director of the Stanford Cell Sciences Imaging Facility (CSIF).

At the CSIF, Stanford researchers can use state-of-the-art light and electron microscopes, get training on the microscopes, and get advice and assistance on how to prepare their samples and interpret their data.

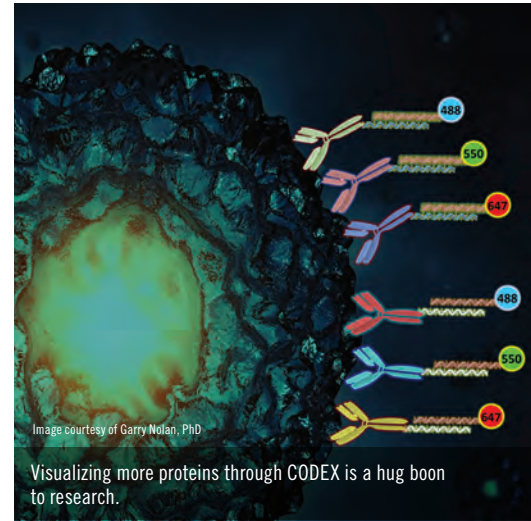
“Most biology labs have a light microscope,” says Mulholland. “What we offer is very high-end imaging that lets researchers do more unique and advanced things.”

Mulholland says that SCI faculty often rely on the central microscopy resource to study the very basic biology of cancer— if there’s a protein suspected of playing a role in cancer, for instance, they might use confocal or super-resolution fluorescence microscopy to see exactly where in cancer cells the protein localizes and what other proteins it interacts with and when. These questions are integral to how a cancer grows and spreads in the body.

Stanford scientists in the lab of SCI member Garry Nolan, PhD, developed the CODEX (co-detection by indexing) approach to be able to fluorescently label and visualize around 50 different proteins in a single tissue sample. In most classic fluorescence experiments, researchers are limited to seeing about five distinct proteins at once, each labeled with a different color fluorescent tag. For understanding cancer cells—which can have dozens of molecular players interacting in many ways— this leap to being able to see more proteins is a huge boon to research.

In CODEX, a tissue slice is labelled with up to 50 antibodies, each of which binds to a specific individual protein or other cellular target. Each antibody also has a short, unique DNA segment that acts as its barcode. Then, one of three fluorescent colors—green, orange or red—is assigned to each barcode. Using iterative cycles, each revealing the locations of three proteins, researchers can work their way through all 50 targets to reveal their locations in a sample. Between each round of probing and visualization, the probes are washed away and a new set of three fluorescent-tagged complementary DNA tags is applied.

The whole CODEX system is engineered to fit inside a small microfluidics device that sits on the microscope— that means the sample never shifts during sequential rounds,



and each picture showing three probes can ultimately be combined into one image that shows many more proteins throughout the tissue.

“Since you can see where various classes of cells are simultaneously positioned, you can start to make hypotheses about interactions between those cells, and whole networks of cells,” says SCI member Peter Jackson, PhD, professor of microbiology and immunology, who has worked with CODEX in his own lab. This gives researchers insight into what molecular markers on cells might be useful to target with anti-cancer drugs. It also lets them compare how different classes of cancer cells change— or disappear— after different treatments, which can shed light on why some drugs work better for some patients than others.

The setup for CODEX is expected to be available in the CSIF by the end of 2018, thanks to funding from multiple sources, including the SCI.

“It’s a really nice synergistic story about it all coming together,” says Mulholland. ■

Some Tumors May Be Born to Be Bad

Pioneering New Models of Tumor Progression

Tumor progression is assumed to be driven by ongoing mutation accumulation and selection, but researchers at the Stanford Cancer Institute have found that some tumors may be destined to invade or metastasize from the outset — they are “born to be bad.”

SCI member Christina Curtis, PhD, MSc, assistant professor of medicine (oncology) and of genetics, is pioneering the way for her “big bang” model, which proposes that mutations that occur during the earliest steps of tumor formation may determine how a tumor will progress.

Curtis’s research focuses on computational biology, which comprises the fields of computer

science and biology. Curtis describes computational biology as bringing “a quantitative understanding to the needs of biological data.” “It’s a really exciting time in the field because we are generating a deluge of high-dimensional data, and quantitative tools are becoming increasingly important for uncovering new biology,” she said.

Understanding the ways that tumors change as they grow, are exposed to therapy, and what enables some cancers to spread to distant tissue sites is challenging since we only see the end products of these processes.

While direct measurement of human tumor progression is not feasible, by analyzing patient genomic data at unprecedented resolution and by simulating the growth of realistically sized tumors (composed of 10s of billions of cells), Curtis found that once a tumor was established, there did not necessarily need to be ongoing selection for additional mutations. “In fact, the tumor cells might already be so highly ‘adapted’ for their environment at an early stage that the tumor may already have what it needs to grow, invade surrounding tissue and potentially even spread to distant organs. It turns the table on how we think about tumor progression.”

Curtis explained that this alternative model and the original model of tumor progression have different prevalence across tumor types and disease stages. However, the “big

bang” model adds motivation for detecting cancer at the earliest possible stage. “We study the whole continuum of tumor progression from initiation to metastasis, but because of our recent findings, we are increasingly interested in earlier detection,” Curtis said.

An essential part of Curtis’s work is delineating the life history of different tumors in order to learn cancer’s evolutionary rulebook. “If we understand these rules, we might be able to anticipate what the tumor might do next and, in turn, how we need to intervene in response,” she said. “One of the biggest challenges is understanding which tumors are aggressive versus indolent. We have few biomarkers for that, but know that not all tumors behave the same. We need to be able to identify the tumors that are born to be bad — destined, for example, to metastasize.”

Curtis recently received a National Institutes of Health (NIH) Pioneer Award, which supports scientists with outstanding records of pioneering approaches to major challenges in research.

“The beauty of this award is that it allows me to test bold hypotheses using new technological and systems biology approaches,” Curtis said. “[The award] speaks to the NIH’s support for the application of computational approaches to better understand mechanisms of cancer development and progression.” ■

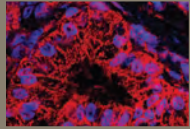


Christina Curtis, PhD



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1



Pancreas Cancer
Research Group
Unites Scientists

4



Pioneering New
Models of Tumor
Progression

7

News

Stanford Cancer Institute News

FALL 2018

New Grant Will Explore Hereditary Cancer Syndrome

Colorectal cancer is the third highest cause of cancer death in the United States. Familial adenomatous polyposis (FAP), a hereditary colon cancer syndrome, causes hundreds of polyps in the colons of affected individuals and a 100% lifetime risk of colorectal cancer. SCI



James Ford, MD

members James Ford, MD, professor of medicine (oncology) and of genetics,

and Michael Snyder, PhD, professor and chair of genetics, have received a significant grant of \$1.6M per year for 5 years from the NIH to study this condition. This Pre-Cancer Atlas (PCA) Research Center project is part of the Human Tumor Atlas Network, and a component of the Beau Biden Cancer Moonshot initiative of the NCI.

Ford and Snyder's grant describes a novel strategy of performing multi-omic characterization and data analysis on polyps of FAP patients. The data the

research team uncovers is expected to greatly facilitate the understanding of colorectal cancer at its earliest stages, with the information being generalizable to FAP patients as well as patients with sporadic colorectal cancer. Establishing novel genetic, epigenetic, metabolic, and proteomic causes of disease progression could be exploited to develop new preventive and treatment strategies. This research may also serve as a model for understanding precancerous lesions of other solid tumors. ■