

AAAS Annual Meeting: Cancer-Related Highlights

Here are hints from this year's American Association for the Advancement of Science meeting about what may be looming on the horizon for oncology.

By Andrew Holtz

Tarnished Outlook for Genetic Silver Bullets

The daunting complexity of living beings is forcing gene researchers to sigh, and then redouble their efforts to get a handle on the genetic mutations that underlie cancer. Hopes are dimming that they will ever find a few critical genetic switches that could turn off tumor growth.

Leona Samson, PhD, American Cancer Society Research Professor and Professor of Toxicology at MIT, says her team went looking for genes that were up-regulated or down-regulated when cells were hit with chemical or ultraviolet damage.



Leona Samson, PhD: "Being in an environment with engineers, who think very differently than biologists, I think is going to be an important merging of disciplines, in order to figure out how to apply analyses of systems to biologic systems."

"We expected to see a few dozen, but we saw 2,000; and that absolutely floored us," Dr. Samson said.

Lawrence Loeb, MD, PhD, of the University of Washington, said evidence is mounting that by the time tumors become clinically apparent their cells contain thousands of mutations. What's more, these mutations appear to be random.

"If you have an enormous number of random mutations, it's not good for human cancers, because it means most of the drugs you're going to use are going to be thwarted by the fact that you already have resistant mutants in every tumor that you

are going to treat," Dr. Loeb said.

"It provides a rationale for multiple therapies, because you have a better chance of hitting more cells that are resistant to one agent."

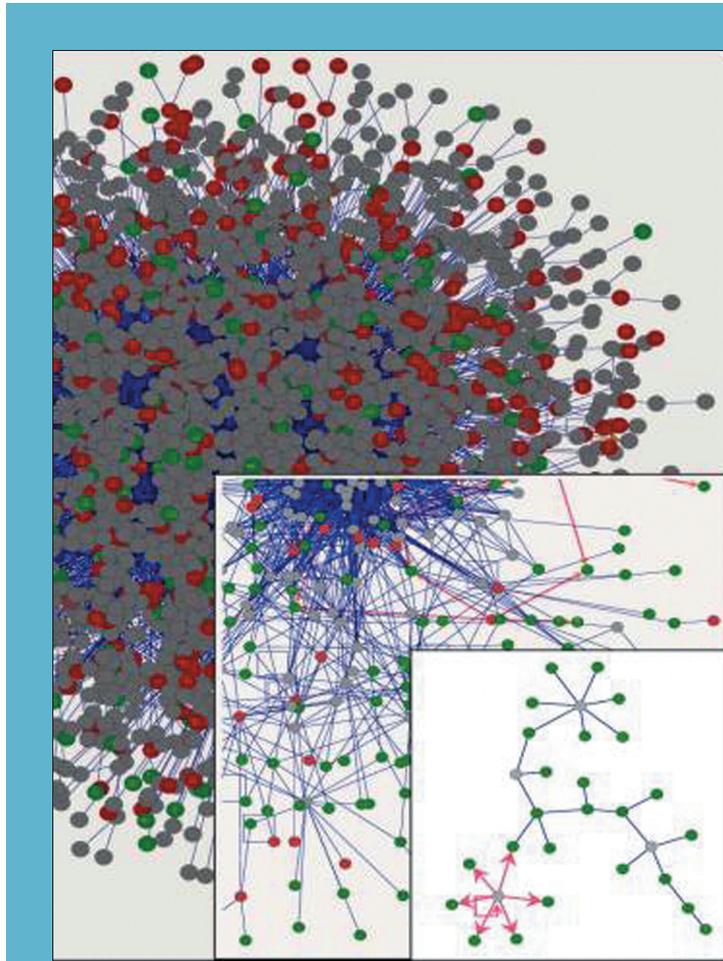
In addition, he said, this emerging paradigm of tumor cell mutation argues in favor of developing personalized cancer vaccines, rather than searching for generic markers to stimulate an immune attack on tumors. Instead of trying to wipe out tumors with new gene-based weapons, a more realistic approach would be to try reducing the rate of mutation.

Dr. Loeb noted that after cells are damaged by environmental assaults, decades often pass before tumors are noticed. For instance, smokers who become addicted in their early teens don't develop symptoms from lung or other cancers until middle age or later.

Therefore, if the rate of mutation in damaged cells could be reduced, perhaps these tumors would not become clinically significant until much later in life.

Dr. Loeb said this concept still needs to be proven; that researchers are still looking for evidence that the proliferation of mutations drives tumor progression. Nevertheless, he said, dreams of uncovering genetic master switches appear to be fading.

"This argument holds very little hope for that idea, unfortunately," Dr. Loeb said.



This visualization of how cellular pathways function and interact to respond to environmental assault was generated by Thomas Begley, PhD, in MIT's Center for Environmental Health using Trey Ideker's Cytoscape software. Leona Samson, PhD, notes that using this type of software, the thousands upon thousands of data points on DNA and protein interactions can be expressed graphically, allowing researchers to see the big picture, while still capturing individual interactions and pathways. "I think it's going to be very important to the field, to have these visualization tools that can help people understand what's going on," she says.

In cancer labs, research biologists are learning to cope. "The system is just a whole lot more complex," Dr. Samson said. "We can't think in terms of one gene and one pathway. We have to understand how all the pathways integrate and talk to each other."

400,000 Data Points

Dr. Samson reviewed the challenges of making sense of all the cellular interactions and responses to environmental assaults. One experiment exposed colonies of *Saccharomyces cerevisiae* yeast to one of four DNA-damaging attacks: three chemicals and ultraviolet radiation.

The researchers found themselves swamped with some 400,000 data points, said Dr. Samson, who has joined with systems engineers and others for help.

"Being in an environment with engineers, who think very differently than biologists, I think is going to be an important merging of disciplines, in order to figure out how to apply analyses of systems to biologic systems," she said.

Biologists also need new ways to see what their data is trying to tell them, so that

rather than being blinded by a blizzard of data, they can begin to see important patterns.

Among the visualization tools her team uses is a software program called Cytoscape, developed by Trey Ideker, PhD, MEng, at the University of California-San Diego, and others.

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Child Abuse & Cancer

Could child abuse increase cancer risk? In a presentation on the broad health consequences of child abuse, Frank W. Putnam, MD, of Cincinnati Children's Hospital Medical Center, summarized links that have been observed between abuse and cancer, as well as other diseases.

The association isn't a complete surprise, though, he noted. Survivors of abuse have higher rates of mental health problems and unhealthy behaviors linked to cancer, including smoking, poor diet, sexually transmitted diseases, and inactivity.



Among the questions that David Spiegel, MD, is investigating is the disruption of normal circadian rhythms in cortisol levels and how that may be associated with cancer outcomes. In patients with depression, for example, cortisol levels are elevated throughout the day; while in those with post-traumatic stress disorder cortisol levels are lower than normal.

But there may be more going on than just a straight-line relationship between risk behaviors and cancer. In response to a question, Dr. Putnam said there may be indications of some excess risk above the level that can be attributed to known risk factors.

Other research into connections between socioeconomic factors, education, social networks, and health also produce relative risk figures that cannot be entirely explained by behavior or medical care.

While research continues into the magnitude and mechanisms of links between child abuse and health outcomes, Dr. Putnam emphasized the benefits of interventions that can



Mustafa al'Absi, PhD, is looking into how the hypothalamus, pituitary, and adrenal glands respond to stress, and then how that response is correlated with smoking cessation or relapse.

reduce child abuse rates.

For example, he said, visits by nurses to homes of high-risk families appear to be effective. Dr. Putnam also presented an analysis that calculated that each dollar spent on such family interventions could save society four dollars in both direct and indirect costs related to the consequences of child abuse.

Stress Management & Cancer

Research into stress, the immune system, and cancer is becoming more sophisticated, according to data presented at the meeting.

Michael Stefanek, PhD, Chief of the Basic Biobehavioral Research Branch at the National Cancer Institute, conceded that there has been some sloppy history in this area: "One of the things that's happening now, that didn't happen historically, is controlling for known risk factors and treatment factors."

Methods of new trials show how things are changing, he said. "You can see that they are trying to make sure that those variables are controlled for: differences in chemotherapy, differences in adherence to medication, things of that sort. So the rigor with which the studies are being done is much better."

Researchers also have access to better measurement tools. For example, researchers have had to resort to repeated blood draws to track corti-

sol levels in study participants, or settle for urinary cortisol measurements, which couldn't provide rapid snapshots of changes; but now salivary cortisol tests allow easier tracking of cortisol responses to stress or other factors.

Cortisol responses and sleep deprivation were among the common themes of new trials on stress and health described at the AAAS meeting.

Researchers in this area hope to produce results that will bridge the extreme reactions they usually get from those who dismiss stress as irrelevant to cancer on the one hand, to those who believe stress by itself can produce lethal

tumors.

"I would hope that we'd get better and get more systematic," said Stanford University researcher David Spiegel, MD. "I think the field has moved that way. We're doing more randomized controlled trials than we used to. We're getting more sophisticated and looking at mechanisms that mediate between psychosocial factors and health.

"If there's a connection, you ought to be able to identify what it is. Whereas a lot of psychosocial work used to be just claims, we're now doing it the way people in oncology do their work."

Among the questions that Dr. Spiegel, who is the Jack, Lulu & Sam Willson Professor in the School of Medicine and Associate Chair of the Department of Psychiatry and Behavioral Sciences, is investigating is the disruption of normal circadian rhythms in cortisol levels and how that may be associated with cancer outcomes.

He said that in patients with depression, cortisol levels are elevated throughout the day; while in those with post-traumatic stress disorder cortisol levels are lower than normal.

Dr. Spiegel noted that his current trials use measurements that are similar to those described by another presenter at the meeting, Michael H. Antoni, PhD, of the University of Miami, which should make their results easier to compare.

Dr. Antoni said that while it has been known for some time that stress and certain measures of immune function are associated in healthy individuals, his team wants to see if stress affects disease outcomes.

In one trial, participants are randomized to receive either a 10-week group training course or a one-day seminar. Stress responses, mood, and health outcomes will be measured at 10 weeks, and at six, 12, and 18 months.

"We are systematically checking in HIV-positive men, women at risk for cervical cancer, and other populations, including breast cancer patients and prostate cancer patients, to see whether or not being in one of these groups, in a randomized trial, affects your perceived stress levels and depression, if it improves your social support and your coping skills, and does it change the levels of cortisol and other stress hormones measured in blood, urine and saliva," he said.



Could child abuse increase cancer risk? In a presentation on the broad health consequences of child abuse, Frank W. Putnam, MD, summarized links that have been observed between abuse and cancer, as well as other diseases. The association isn't a complete surprise, though, he noted, since survivors of abuse have higher rates of mental health problems and unhealthy behaviors linked to cancer such as smoking, poor diet, sexually transmitted diseases, and inactivity.

While important questions about stress and cancer progression are being investigated, Dr. Antoni said oncologists have a responsibility to address the mental health consequences of cancer diagnoses and treatments.

"I think clinicians need to focus on the patient's quality of life first. If the patient is experiencing decreased quality of life related to cancer diagnosis or treatment, a responsible clinician will refer them to a psychologist or psychiatrist for some type of an intervention," Dr. Antoni said.

Stress also plays a central role in the leading preventable cause of cancer: smoking. Mustafa al'Absi, PhD, at the University of Minnesota in Duluth, is

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"If you have an enormous number of random mutations, it's not good for human cancers, because it means most of the drugs used will be thwarted by the fact that there are already resistant mutants in every tumor that will be treated. It provides a rationale for multiple therapies, because you have a better chance of hitting more cells that are resistant to one agent."

SGO Annual Meeting

Low-Risk Cervical Cancer: Minimal Benefit from Adjuvant Chemo

By Robert H. Carlson

SAN DIEGO—Most so-called high-risk patients with cervical cancer do not benefit from adjuvant therapy after radical hysterectomy, because they are already cured without it. So said experts speaking here at the Society of Gynecologic Oncologists Annual Meeting in a plenary session.

In other patients the disease recurs despite adjuvant treatment. And others, a minority, suffer lasting injury from adjuvant treatment. Researchers discussed data for clinicians to consider when making the decision whether or not to treat adjuvantly.

Investigators conducting a retrospective in-depth analysis of the earlier prospective Intergroup Southwest Oncology Group 8797/Gynecologic Oncology Group 109 trial said that study determined that women at high risk of relapse due to tumor size or nodal status after hysterectomy for cervical cancer can significantly benefit from chemotherapy added to adjuvant radiotherapy regardless of age, tumor histology, or tumor grade.

As reported by first author Samuel Im, MD, a fellow in gynecologic oncology at the University of California, Irvine, the retrospective study now shows that chemotherapy appeared to add little benefit to radiation for low-risk women in the prospective trial who had tumors of 2 cm or less and no more than one involved node.

The randomized trial had included 243 patients with Stages IA2, IB, or IIA cervical cancer and histologically confirmed pelvic lymph node involvement who underwent radical hysterectomy and pelvic lymphadenectomy. Patients



Samuel Im, MD, reported that the retrospective study now shows that chemotherapy appeared to add little benefit to radiation for low-risk women in the prospective Intergroup SWOG/GOG trial who had tumors of 2 cm or less and no more than one involved node.

were also categorized as having parametrial extensions or positive surgical margins after surgery.

Subjects were randomized to receive either pelvic radiation (116 patients) or radiation with cisplatin at 70 mg/m² plus a 96-hour infusion of fluorouracil at 1,000 mg/m² every three weeks for four cycles (127 patients).

Dr. Im said the SWOG/GOG researchers found a significant improvement in progression-free survival (63% to 80%) and four-year overall survival (71% to 80%) for patients receiving adjuvant chemotherapy and radiotherapy compared with radiotherapy alone.

The reanalysis now indicates that there was a significant survival advantage to adding chemotherapy to radia-

tion therapy for women with two or more positive nodes, Dr. Im reported.

"However, for the one positive-node group, the survival for radiation alone appeared to be as good [as the radiation-chemotherapy group] and showed no significant advantage by adding chemotherapy."

He said women in the earlier randomized trial who had one positive node and were treated with chemotherapy and radiation experienced only a four percentage-point improvement in five-year survival over those who received radiotherapy alone (83% versus 79%, respectively).

But women with two or more positive pelvic nodes saw a 20 percentage-point improvement in five-year survival when they received chemoradiotherapy compared with radiotherapy alone (75% vs 55%, respectively).

Dr. Im also reported that women in the randomized trial who had tumors larger than 2.0 cm experienced a 19% improvement in five-year survival compared with those in the radiotherapy-alone group.

Challenging Decisions

The commentator for the paper, Anthony H. Russell, MD, Head of the Gynecology Oncology Service at Massachusetts General Hospital, said, "Selecting which patients should receive adjuvant therapy, what modalities they should be treated with, and at what intensity constitute some of the most challenging decisions we face as physicians."

But he said Dr. Im's study illustrates some of the difficulties with a univariate analysis on subsets of patients from a larger study.

"If one examines the whole pattern of recurrence reported in this manuscript, one could conclude that local failures are substantially more common than distant failures—almost twice as common—and that chemotherapy had no impact on the probability of distant failure, which was actually slightly higher in the group that received combined modality adjuvant therapy," Dr. Russell said.

He also pointed out that the entire benefit of chemotherapy appeared to be due to enhanced tumor control within the irradiated volume, which he said represented an approximate one-third reduction in the risk of local failure.

Dr. Im responded that his was a reanalysis of a study designed for different purposes and that he and his colleagues did not run a multivariate analysis.

Dr. Russell then asked the perennial question, "If the patient treated for a Grade 3 adenocarcinoma with parametrial extension and a positive margin and metastasis to only one node were your sister, would you recommend treatment with the radio- and chemotherapy?"

Dr. Im joked that he only had a brother. He then noted that this reanalysis looked only for women who would not need the double adjuvant therapy and not specifically for those who should receive it.

But he added that the randomized study had suggested that women with positive parametrial involvement should receive the additional treatment. 

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looking into how the hypothalamus, pituitary, and adrenal glands (known as the HPA axis) respond to stress, and then how that response is correlated with smoking cessation or relapse.

Dr. al'Absi said there are clear gender differences. In women who quit smoking, the length of time they remained abstinent was inversely correlated to their withdrawal symptoms; however there was no correlation with cortisol response.

On the other hand, abstinence duration in men was correlated with cortisol response, but not withdrawal symptoms. Despite the differing reactions to smoking cessation by male and female participants in the study, there

was no significant difference in measures of either smoking or cessation success rates.

Sound's Hot

Focused beams of high-energy ultrasound can cook targets within the body without damaging tissue between the target and the ultrasound transducer. However, investigators are still waiting for therapeutic ultrasound to come to a boil.

Researchers at the Institute of Cancer Research and Royal Marsden Hospital in Sutton, England, are testing their ability to selectively destroy individual tumors in patients with liver or kidney cancer who have failed to respond to all other therapies.

These Phase I and II trials are not intended to cure patients, but just to

observe the effects of the high-energy ultrasound beams.

Ultimately, therapeutic ultrasound could spare some patients from invasive conventional surgery, according to Gail R. ter Haar, PhD. And if the technique is well tolerated by patients, it could be used repeatedly as new tumors arise.

"Broadly speaking, if we can image a tumor, we can treat it," Dr. ter Haar said.

However, the ultrasound energy cannot pass through air pockets, which limits its application to lung tumors. Bone is also a poor conductor of ultrasound, which means that it will be difficult to apply the technique to brain tumors.

Dr. ter Haar noted that in China some 3,000 patients have undergone therapeutic ultrasound procedures.

However, she said the treatments have not been part of controlled research trials, so more work remains to be done before therapeutic ultrasound can be compared with other cancer treatments.

Therapeutic ultrasound devices are also commercially available in France. Jean-Yves Chapelon, PhD, with INSERM in Lyon, France, said their Ablatherm devices are usually used to treat older prostate cancer patients who are not candidates for conventional surgery.

Rather than trying to pinpoint tumors, the entire prostate is ablated.

Dr. Chapelon said he thinks their technique will eventually challenge other prostate cancer techniques, but that they are still gathering the type of outcomes data needed to convince practitioners to adopt therapeutic ultrasound. 