

GEMS meeting focuses on preventing and curing cancer

By William Kaufmann and Eddy Ball

The [Genetics and Environmental Mutagenesis Society \(GEMS\)](http://www.gems-nc.org/)

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held its 31st annual fall meeting Nov. 14 at the Sheraton Imperial Hotel and Convention Center in Research Triangle Park, N.C. The meeting, supported in part by grants from NIEHS, was organized around the theme "Exploiting the DNA damage response to prevent and cure cancer."

The event was organized and moderated by GEMS President-elect [William Kaufmann, Ph.D.](http://unclineberger.org/members/william-k-kaufmann),

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who opened the meeting on an optimistic note. "We'd all like to find a way we can prevent or cure it [cancer]," he said. "It's a rather lofty goal, but one we know is attainable."

"A large fraction of cancers are cured simply by surgery," he explained. The metastases that escape the surgeon's knife represent our biggest problem."

"The other side of it is prevention," Kaufmann continued. A great part of the challenge is identifying exposures and metabolic processes that can be manipulated to stop cancer before it has a chance to begin.

DNA damage responses: bedside to bench to bedside

Opening the program, Kaufmann introduced [Michael Kastan, M.D., Ph.D.](http://pharmacology.mc.duke.edu/faculty/kastan.html),

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of Duke University, who described his work to translate discoveries about *TP53* and *ATM* to more effective treatments for cancer. He introduced an important new role of nucleolin in nucleosomal remodeling in support of repair of DNA double-strand breaks, and described the application of inhibitors or activators of p53 and ATM signaling to enhance therapy for cancer.

Pathways of DNA repair, and DNA damage checkpoints, protect against development of cancer, by reducing the levels of DNA damage or enhancing the time available for repair of the damage. These DNA damage responses not only protect against the development of cancer, but also protect cancer cells from radiation and chemotherapies that seek to cure the disease. The demonstration of synthetic lethalties, where a weakly toxic insult can be transformed into a highly toxic lesion by modification of gene expression, has renewed interest in the DNA damage response. Inhibitors of poly(ADP-ribose) polymerase have modest toxicity normally but, in cells with inactivation of BRCA1-dependent homologous recombination, these drugs have massive toxicity. New combinations of drugs to kill cancer cells with greater specificity are being developed.

Potentiating Top1 poisons by modulating the DNA damage response

The meeting's second speaker, [William Gmeiner, Ph.D.](http://www.wakehealth.edu/faculty/Gmeiner-William-Henry.htm),

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of Wake Forest School of Medicine, described his efforts to make 5-fluorouracil a more effective chemotherapeutic drug, by creating polymers of the drug with longer lasting bioavailability. The improved polymers produce DNA lesions that bind DNA topoisomerase I (Top1) for enhanced cell killing, and are now being tested for more effective treatment of leukemia and lymphoma.

A remarkable discovery in the field of environmental carcinogenesis was the demonstration that the XPA nucleotide excision repair (NER) factor varied in its expression according to the time of day. Circadian regulation of NER in skin implies that human risk of skin cancer may vary with the time of harmful UV exposure. Circadian regulation of NER may also influence the efficacy of chemotherapies, and this implies that the timing of treatment - and standard of care - may need to be modified.

Control of DNA repair and cancer by the circadian clock

The final speaker of the day, [Aziz Sançar, M.D., Ph.D.](http://www.med.unc.edu/biochem/asancar),

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of the University of North Carolina at Chapel Hill (UNC), reported on his efforts to define the role of the circadian clock in



"Cancer can be prevented," Kaufmann assured the audience. That positive approach motivated Kaufmann to design the two-part series of meetings in 2013 that highlighted mechanisms of environmental carcinogenesis during the GEMS spring meeting (see [story](#)) and strategies for prevention and cure at the fall meeting. (Photo courtesy of Steve McCaw)

environmental carcinogenesis, and how clock mechanisms may be exploited to prevent or cure cancer.

Importantly, mice treated with UV, at a time of day when skin DNA repair was high and DNA replication was low, developed one-fifth as many skin cancers as mice treated twelve hours later, when DNA repair was low and DNA replication was high. Susceptibility to skin carcinogenesis varies according to the time of day in mice, and studies are underway to determine whether human skin also displays circadian variation in risk of UV carcinogenesis.

(William Kaufmann, Ph.D., is a professor in the Department of Pathology and Laboratory Medicine, and a member of the Cancer Genetics Program at UNC.)

Nurturing the next generation

The GEMS fall meeting also featured four short talks and eight poster presentations by students and postdoctoral fellows. Judges selected first place winners in both categories.

- Jonathan Hall, Ph.D., of North Carolina State University, won best short talk. Along with his plaque, Hall received a \$1,000 award to attend the 2014 Environmental Mutagenesis and Genomics Society meeting in Orlando, Fla. A trainee in the NIEHS-funded Cell Signaling and Cancer Group headed by [Robert Smart, Ph.D.](http://tox.sciences.ncsu.edu/people/robert-c-smart/), (<http://tox.sciences.ncsu.edu/people/robert-c-smart/>) Hall spoke on CCAAT/enhancer binding protein (C/EBP) regulation of p21CIP1/WAF1 proteins during the UVB-induced DNA damage checkpoint response.
- Scott Lujan, Ph.D., of NIEHS, won a \$100 check for best poster presentation. A trainee in the DNA Replication Fidelity Group headed by lead researcher and structural biologist, Lujan presented findings from his work, "Genome architecture and dynamics drive mutagenesis via replication infidelity." Lujan was first author on the study, a collaboration among 11 structural biologists, molecular geneticists, and biostatisticians at NIEHS.



Like many researchers and clinicians, Kastan is searching for the right combination of drugs to target cancer with as much efficacy and as few side effects as possible. (Photo courtesy of Steve McCaw)



Kaufmann, left, started off the question-and-answer session that followed Sancar's presentation. Sancar is a distinguished professor of biochemistry and biophysics at UNC. (Photo courtesy of Steve McCaw)



Gmeiner is professor of physiology and pharmacology in the Cancer Biology Comprehensive Cancer Center and Brain Tumor Center of Excellence at Wake Forest School of Medicine. (Photo courtesy of Steve McCaw)



Toxicologist Stephanie Smith-Roe, Ph.D., was one of many scientists from NTP and NIEHS attending the meeting. (Photo courtesy of Steve McCaw)



NIEHS Scientific Review Officer Rose Anne McGee was recognized for her work as treasurer. She has also served as president of GEMS. (Photo courtesy of Steve McCaw)



Among board members honored for their service by GEMS President Thomas Hughes, right, was retired NTP scientist Barbara Shane, Ph.D., a 2011-2013 GEMS councilor. (Photo courtesy of Steve McCaw)



The climax of the awards ceremony was the presentation of a plaque and travel award to Hall for best short talk. (Photo courtesy of Steve McCaw)



After recognizing their board members, Kaufmann and Hughes presented honors to the first of their rising stars, Lujan, center. (Photo courtesy of Steve McCaw)

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