AMERICAN CHEMICAL SOCIETY DIVISION of
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Newsletter

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Editor, Laurie Davenport

2015 Founder's Award winner – Arthur Grollman

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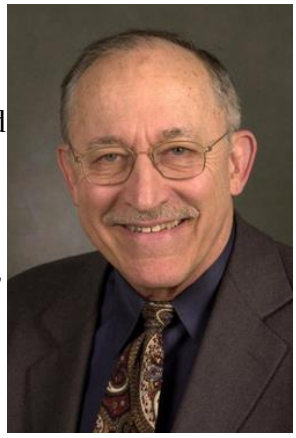
Dr. Arthur P. Grollman the recipient of this year's Founder's Award. Dr. Grollman is Distinguished Professor of Pharmacological Sciences and Glick Professor of Experimental Medicine at Stony Brook University. He is also Director of the Leo and Judy Zickler Laboratory of Chemical Biology in the Department of Pharmacological Sciences.



Dr. Grollman has published more than 200 papers in the fields of molecular biology and cancer research. His research interests have focused on the biological consequences of DNA damage as they relate to molecular mechanisms of DNA replication, mutagenesis, and DNA repair. Research in the Grollman laboratory was instrumental in establishing the molecular mechanism of action of antitiumor agents, including bleomycin, which was shown to generate strand cleavage through a unique, iron-catalyzed, radical mechanism after selectively binding to specific sequences in DNA.

Grollman's studies on site-specific mutagenesis of DNA adducts represent an important scientific advance. His work in this area led the way in establishing the mutagenic specificity of single DNA lesions. Grollman and co-workers established that certain DNA polymerases incorporate dAMP and dCMP opposite 8-oxoguanine; this work proved to be key to interpreting the mutagenic spectrum induced by this frequently oxidized base. Subsequent studies of 8-oxoguanine repair led to the formulation by Grollman & Miller of the GO pathway, which protects cells against mutations produced by oxidative DNA damage. Grollman and his collaborators also made landmark contributions to our current understanding of the molecular mechanisms by which DNA repair proteins, including DNA glycosylases, DNA polymerases and endonucleases, process oxidative DNA damage.

In 2005, following his long-term interests in environmental toxicology, Grollman turned his attention to the etiology of Balkan endemic nephropathy (BEN), an endemic kidney disease associated with carcinomas of the upper urothelial tract (UTUC). Adopting a molecular epidemiologic approach, he and his associates identified aristolochic acid, a nephrotoxic, carcinogenic component of the Aristolochia plant, as a prominent contaminant of the home

baked bread ingested by residents of the endemic region. In doing so, he established the proximate cause of a devastasting environmental disease for which 100,000 residents of the endemic region are believed to be at risk. As a result of Grollman's research, appropriate public health measures have been undertaken in the Balkans and BEN has been renamed aristolochic acid nephropathy.

Recognizing that Aristolochia herbs have been used for centuries in Traditional Chinese Medicine, Grollman conducted studies in Asia, specifically in Taiwan, where the incidence of UTUC and kidney disease is the highest in the world. Using robust biomarkers identified in his studies of BEN, including a unique "signature mutation" for aristolochic acid, the group showed that the major risk factor for UTUC in Taiwan relates to the medicinal use of Aristolochia herbs. As the mode of usage of Aristolochia in mainland China is identical to that in Taiwan, it is likely that tens of millions of Taiwanese and Chinese are currently at risk.

Recognizing the impact on global health that could result from the extensive past usage of Aristolochia herbs, Grollman currently leads an effort, in collaboration with Bert Vogelstein (Johns Hopkins) to develop minimally-invasive biomarker-based tests for early detection of mutated DNA in populations at risk. This novel genomic approach is directly applicable to screening for bladder cancer in the US and throughout the world.

Dr. Grollman is a recognized expert on the clinical pharmacology of herbal medicines and has testified on this subject before the White House Commission on Alternative and Complementary Health Policy, the Senate Subcommittee on Commerce, Science and Transportation and the Governor of New York's Task Force on Life and Law.

He has lectured throughout the world and served on numerous scientific advisory committees and boards, including those associated with the American Cancer Society, National Institute for Environmental Health Sciences, and American Association of Medical Colleges.

His honors include a MERIT award from the National Cancer Institute, two American Cancer Society Scholarships in Cancer Research, the Environmental Mutagenesis and Genomics Society Award, and the Princess Takamatsu Cancer Research Fund-International Lectureship

Grollman received his B.A. in Chemistry from the University of California at Berkeley and his M.D. from the Johns Hopkins School of Medicine. Following an internship and residency in Internal Medicine at Johns Hopkins, he conducted research at the National Institutes of Health. He then joined the faculty of the Albert Einstein College of Medicine, Bronx, N.Y., where he rose through the ranks to become Professor of Medicine, Pharmacology and Molecular Biology. He served concurrently as Associate Dean for Scientific Affairs before moving to Stony Brook University as (founding) Chairman of the Department of Pharmacological Sciences. In 2000, he relinquished his administrative responsibilities as Chair to devote full time to research.

Dr. Grollman also served as Attending Physician in Medicine at hospitals associated with the Albert Einstein College of Medicine and, after 1974, those associated with the Stony Brook School of Medicine. He has held one-year Visiting Professorships at Stanford University, Johns Hopkins School of Medicine, University of California at San Francisco, National Cancer

Research Center (Japan), the Weizmann Institute (Israel), New York University and the U. of Washington.

Chemical toxicology of a novel human carcinogen, aristolochic acid
Abstract for Arthur Grollman's presentation at the 2015 ACS Meeting

Aristolochic acid (AA) is a nitrophenanthrene carboxylic acid found in all plants in the genus *Aristolochia*. The presence of aristolactam (AL)-DNA adducts in human tissues provides a tangible link between exposure to AA and its nephrotoxic and carcinogenic effects. Moreover, the *TP53* mutational spectrum observed in AA-induced upper urinary tract cancers (UTUC) serves as a biomarker of internal exposure. We used these biomarkers to show that AA is the causative agent of Balkan endemic nephropathy, an environmental disease. Globally, human exposure to AA results from the use of *Aristolochia* herbs for medicinal purposes. We have used AL-DNA adducts and their signature TP53 mutation to document the presence of AA-induced UTUC in Taiwan, China and other populations at risk. AA is bioactivated by nitroreduction to form AL-NOH followed by enzymatic sulfonation, which facilitates formation of AL-DNA adducts. These adducts accumulate in human tissues, reaching a steady state level that reflects the balance between AA metabolism, adduct formation and repair. AL-DNA adducts are highly resistant to global genomic nucleotide excision repair, accounting for the strong strand bias and their remarkable, decade-long persistence in human tissues. Translesional DNA synthesis past AL-DNA adducts generates predominantly A:T> T:A tranversions. Whole exome sequencing of AA-induced UTUC reveals a unique, genome-wide mutational signature characterized by a high mutational load with an excess of A:T to T:A transversions and splice acceptor mutations, and by enrichment of A>T mutations on the nontranscribed strand with an A>T preference for a T/CAG sequence context. This mutational signature has been used to identify candidate driver genes and to generate a panel of genes for screening serum and urine in individuals at risk of developing AA-UTUC. Thus, we have combined mechanistic investigations with a molecular epidemiologic approach to establish causative linkages between exposure to AA and increased risk for renal disease and cancer.