Meeting Report

The 2008 American Federation for Aging Annual Research Conference: Aging and Cancer: Two Sides of the Same Coin?

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The 2008 Research Conference of the American Federation for Aging Research took place in New York City on October 6–7 and had, as its theme, the interface between the biology of cancer and the biology of aging. The first day was devoted to a series of 5-year progress reports by grantees of an innovative program jointly sponsored by the National Cancer Institute and the National Institute on Aging aimed at fostering both basic and clinical interactions and integrations among investigators with primary research interests in either the biology of aging or the biology of cancer. This was followed by a series of presentations on cell biology (Judith Campisi), evolutionary biology (Steven N. Austad), mitochondrial damage (Lawrence A. Loeb), stem cell functionality (Thomas A. Rando), oxidative stress and cancer resistance (Rochelle Buffenstein), signal transduction and replicative senescence in cancer and aging (Norman E. Sharpless), and telomere biology (Jack D. Griffith). Overview presentations were given by John W. Rowe and Harvey Jay Cohen. The conference closed with a roundtable discussion with representatives of industry in an effort to enhance communications with academicians.

Key Words: Cancer—Demography—Comparative biology—Mutation—Secretory phenotype—Stem cells—Telomeres—AFAR—Industry.

A S with so many issues in biogerontology, the most satisfying understanding of why there is a coupling of cancer to aging comes from evolutionary biological considerations. Researches from the Campisi and Sharpless laboratories continue to support the notion of antagonistic pleiotropy. Early life course gene actions have been selected to attenuate somatic proliferation via cellular or replicative senescence as a tumor suppression mechanism. Late in the life course, however, when phenotypes will have escaped the force of natural selection, the seeding of tissues with senescent cells can lead to tumor promotion via a “field effect” resulting from their senescence-associated secretory phenotype (SASP). The decline in late life regenerative potential (that involves stem cells and their niches) likely contributes to a variety of senescent phenotypes.

Although childhood forms of cancer are of major clinical significance, the vast majority of human neoplasms appear to be coupled to the biology of aging in that their age-specific incidences begin to rise steadily (and often exponentially) after the emergence of the mature adult phenotype. The same can be said for the majority of neoplasms in all mammalian species in which the relationship has been sufficiently probed. It can be argued (as was pointed out in the special lecture by Harvey Jay Cohen) that, with the apparent exception of adenocarcinomas of the prostate and colon, an initial exponential or near-exponential age-related increase eventually tapers off during the last decades of life. Perhaps, however, this is related to the accompanying atrophy observed in many tissues during aging, with the result that the target cell types have been substantially diminished. So we are faced with this mystery of the mechanism(s) underlying this striking coupling of cancer with aging.

The American Federation for Aging Research (AFAR) Conference on Aging and Cancer did not solve these problems, but did present us with a coherent theory based upon evolutionary biological considerations. Moreover, we heard clear evidence of progress on a number of highly relevant issues such as stem cell biology, mitochondrial biology, and systems biology. There was much that could have been added, notably more information on epigenetic mutations and the numerous disruptions of gene networks that unfold during the genesis of malignant neoplasms.

Our conference commenced with a series of very diverse presentations covering a wide range of issues dealing with the interface of cancer and aging. Readers wishing to learn more about the current status of these innovative programs, which address important clinical as well as basic issues, should contact our speakers: Sanjay Asthan, University of
Wisconsin–Madison; Nathan Berger, Case Western Reserve University; George Bosi, Memorial Sloan-Kettering Cancer Center; Gurkanal Chatta, University of Pittsburgh Medical Center; Julie A. Kish, H. Lee Moffitt Cancer Center, Tampa FL; Robert S. Schwartz, University of Colorado Health Science Center; and Robert Wallace, University of Iowa College of Public Health. The author gave a brief presentation representing the University of Washington program, as Peter S. Rabinovitch, the codirector, could not participate. Our moderator was the National Institute on Aging (NIA) director, Richard Hodes, an immunologist who for many years has maintained an active laboratory at the National Cancer Institute. It should be noted, parenthetically, that Huber Warner, the editor in chief of this journal, while leading what is now called the Division of Biology of the NIA, led an effort to bring together these two institutes and their grantees many years ago at a conference in Annapolis, MD, which I had the privilege of attending (1). It was indeed gratifying to learn that that initiative eventually led to a joint grant initiative.

Our more general program began with a lively Keynote address by John W. Rowe, a geriatrician now associated with the Mailman School of Public Health of Columbia University, but formerly the CEO of Aetna. His topic was “The Challenges and Opportunities of an Aging Society.” His outline of the cultural and economic implications of the demographic trends in our society (lots of old people and fewer young ones to take care of them) was indeed sobering. Cancer has now overtaken heart disease as the major cause of mortality. The need for research on the pathogenetic interface with the biology of aging therefore represents a major challenge and opportunity.

Judy Campisi gave a brilliant overview of current biological research in cancer and aging and presented new data on SASP (the senescence cell–associated secretory phenotype) that was published 2 months after the conference (2). I find her ideas quite compelling, and her efforts to examine these issues in vivo, with a focus on prostatic cancer, is a particularly important new direction.

Steve Austad reviewed the classical evolutionary biological theory of why we age (3) and put cancer and aging in that context. He is now a leader in the comparative biology of aging, a field that promises to reveal much about differential susceptibilities to cancer as well as aging (4). For example, Shelly Buffenstein has pioneered research on the amazingly long-lived naked mole rat (which enjoys a circa eightfold longer maximum life span than comparably sized laboratory mice). Remarkably, she has never observed a cancer in these animals. Most of her recent works have addressed the oxidative damage theory of aging. Naked mole rats appear to tolerate a remarkable degree of such damage to their macromolecules, but such damage does not appear to increase during aging (5).

Larry Loeb, the originator of the mutator phenotype as a key to the development of malignancies, reviewed new data on the characterization of mutations (6). He also reviewed some of my own data, the first to report on the rising frequencies of somatic mutations of an epithelial cell type during aging (7). Larry’s laboratory has pioneered the development of an exquisitely sensitive assay for both nuclear and mitochondrial mutations (8,9). These assays have been applied to the investigations of both cancer and aging (10).

Tom Rando bought us up to date on how stem cell functions change with aging. His work has dealt mainly with skeletal muscle stem cells, but the results are likely to have lessons for a variety of stem cells, particularly the importance of the stem cell microenvironment, or niche (11). He presented new research highlighting the importance of the Wnt as well as the Notch pathways in stem cell behavior during aging (12). Norm Sharpless has long been interested in DNA damage and genes that not only prevent cancer but also compromise organismal fitness by limiting tissue regeneration and repair (13). He reviewed his pioneering studies of how p16(INK4a) not only acts as a tumor suppressor but also diminishes regenerative pathways during aging. This too can be put into the context of the evolutionary biological concept of trade-offs in gene action.

Jack Griffith reviewed his pioneering work on the fine structure of telomeres and the implications for function, both in cancer and in aging. His early work with Titia de Lange has now become a classic in biology (14). His research has expanded to encompass such subjects as the Werner syndrome helicase–exonuclease (15) and the repair of DNA cross-links (16). Jack pointed out that there were some laboratories developing new evidence for novel RNAs associated with telomeres. Thus, we are nowhere near the end of learning about the end of chromosomes and how they contribute to replicative senescence and oncogenesis!

We turned to a master clinician, Harvey Jay Cohen, to sum up what we can learn from “flipping the coin” between cancer and aging. Harvey has thought about this interface during his many years of geriatric practice. He pointed out the many gaps in our understanding of basic science, clinical issues, and societal issues related to that interface (17). For starters, we really have little understanding of the late life declines in the age-specific incidence of many important cancers.

Our meeting ended with a roundtable discussion led by representatives of industry. Among the problems discussed was the fact that only about one in 10 promising therapeutic compounds make it to Phase III clinical trials. G.M.M. also lamented the loss of “curiosity-driven research” in industry.

The AFAR Organizing Committee for this event included Harvey Jay Cohen, George M. Martin, Roger McCarter, Richard L. Sprott, Jean-Luc Vanderheyden, Terrie Fox Wetle, and Margaret Yu. Drs. Wette and Vanderheyden served as discussion moderators. AFAR thanks the conference sponsors: The Glenn Foundation, the Ellison Medical Foundation, Eli Lilly, Myriad Genetics, Pfizer, GE Healthcare, and an anonymous donor. Thanks also to GE Healthcare for having
sponsored a Junior Investigator Award for Excellence in Cancer–Aging Research. These Awards were given during the conference. The winners were Dr. Hiroaki Iwasa, Rutgers, for research on EGF signaling; Dr. Brian Onken, Rutgers, for the development of novel fluorometric indicators of the dietary restriction state and associated studies of Metformin; Dr. Marcella Raices, Salk Institute, for studies of the structure and function of telomeres of Caenorhabditis elegans; and Dr. Christina Yau, Buck Institute and University of California, Berkeley, for gene expression and bioinformatics studies on aging, oxidative stress, and breast cancer.

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