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Meeting Report

The Biological Sciences Section Program at the 60th Annual Meeting of The Gerontological Society of America

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In this era of genomics and other exciting technical advances, research on the biology of aging is undergoing a renaissance. This report summarizes 10 cutting-edge areas of research covered in symposia that spanned such topics as stem cells, novel vaccine strategies, nutritional sensing, new concepts of Parkinson's disease, high throughput screening for aging interventions, manipulating telomerase in cancer and immunodeficiency, synergy between aging and HIV disease, and epigenetic influences on aging. Novel animal models, including those showing no evidence of aging, as well as ethical and political implications of embryonic stem cells and alternative medicine are also discussed.

THE Biological Sciences section program was organized around the theme of the 60th Annual Meeting of The Gerontological Society of America, namely ''The Era of Global Aging: Challenges and Opportunities.'' This report provides a brief summary of the 10 symposia that were part of the Biological Sciences program, which was organized by Dr. Rita B. Effros, David Geffen School of Medicine at UCLA, Los Angeles. The two Presidential Symposia are described first, followed by the other eight symposia.

Stem Cells: Promise, Pitfalls and Potential for Medicine

Chair: Helen Blau, Stanford University, California

The use of stem cells in regenerative medicine is an area of major importance in gerontology. H. Blau first addressed one of the fundamental challenges in stem cell biology, namely, understanding the mechanisms that direct the delicate balance between quiescence, self-renewal, and differentiation. Adult stem cells are localized in specialized microenvironments, or niches, which protect them from differentiation. Upon culture, adult stem cells lose their ''stemness,'' or ability to self-renew. Blau and colleagues have engineered artificial in vitro microenvironments that mimic key biochemical characteristics of adult stem cell niches, and which allow phenotypic and dynamic analyses of thousands of individual cells by time-lapse microscopy. This system has been used to show that single proteins alter proliferation kinetics and asymmetric division behavior, leading to self-renewal in culture. The data demonstrate that parameters of proliferation behavior in vitro correlate with stem cell function assayed in vivo. A. Spradling (Carnegie Institution of Washington, Baltimore, Maryland) discussed new research on the role of competition in maintaining tissue stem cells within the adult *Drosophila*. He showed that many stem cells in ovarian follicles are regularly replaced within their niches by the young daughters of neighboring stem cells, and that replacement is not limited to adjacent stem cells within a single niche. In cases where stem cells in a niche are replaced by cells that have migrated from a different location, the data suggest that this replacement is facilitated if the resident stem cell has sustained a deleterious mutation, and that preferential stem

cell replacement plays an important role in minimizing the long-term accumulation of somatic mutations.

The presentation by J. Campisi (Lawrence Berkeley National Laboratory, Berkeley, California) focused on the process of cellular senescence, which may pose a key limitation to the clinical use of stem cells. She and her colleagues have found that senescent cells, which accumulate with age in mammalian tissues, secrete a large number of proteins (e.g., inflammatory cytokines, growth factors, and extracellular matrix-degrading proteases) that have the ability to alter the tissue microenvironment. Of particular interest, human embryonic stem (hES) cells are typically cultured on human fibroblast ''feeder layers,'' some of which are, in fact, senescent. Recent experiments on human fibroblast feeder layers that do, and do not, support hES stem cell maintenance suggest that the presence of senescent cells in the stem cell niche can suppress stem cell renewal and promote stem cell differentiation. Thus, senescent cells might drive aging phenotypes, in part, by inhibiting stem cell renewal.

The session was capped by A. Charo (University of Wisconsin, Madison), who discussed the political, legal, and ethical issues relevant to stem cell research. The derivation of embryonic stem cells results in the destruction of an embryo, thus triggering opposition by right-to-life proponents, who cite moral and ethical concerns, and by some members of the women's movement who object to the use of stimulating drugs in women who agree to donate eggs for the creation of specialized embryonic stem cell lines. However, recent technological advances have the potential to render both of those objections moot: By introducing four genes into skin fibroblasts, one can generate stem cells that seem to share all the features of embryonic stem cells—but without using or destroying embryos. Dr. Charo raised the possibility that this new research may motivate some groups to advocate for preferential federal funding only for non-embryonic stem cell research; it will certainly complicate any efforts to expand funding for embryonic stem cell research at the federal level.

From Mice to Men: Translating Basic Science to Improve Vaccines in Older Adults

Chair: Janet McElhaney, University of Connecticut and University of British Columbia

In spite of widespread vaccination programs for elderly persons, hospitalization and death rates due to influenza are rising, underscoring the need for improved vaccine strategies, particularly because the current use of antibody titers as a sole measure of vaccine efficacy may be limited in the older adult population. To address this issue, J. McElhaney's research has focused on developing a cellular immune correlate of protection. Her studies have shown that a key mediator of cytotoxic T-lymphocyte (CTL) activity known as granzyme B and the interferon-γ to interleukin-10 ratio produced by T-helper cells correlate with protection against influenza in older people, including those with congestive heart failure. Thus, these measures can be used as an alternate way to evaluate influenza vaccine efficacy. L. Haynes (Trudeau Institute, Saranac Lake, NY) next described how mouse models have been used to both identify the specific immune cells responsible for the decline in influenza vaccine efficacy with aging, and to evaluate possible immunomodulatory strategies. These experiments demonstrated that the impact of aging is greatest on the function of CD4+ T cells. Evaluation of different adjuvants showed that a mixture of the TNFα, IL-1, and IL-6 proinflammatory cytokines, or poly I-C (a Toll-like receptor ligand) added to the vaccine led to a more robust humoral response. Improved vaccine responses were also obtained in mice that received T-helper cells that were primed in vitro to produce IL-17.

B. Grubeck-Loebenstein (Institute for Biomedical Aging Research, Austrian Academy of Sciences, Innsbrück) focused on experiments that provide a potential mechanistic link between the changes in the function of the immune system with aging and the decreased responsiveness to vaccines in elderly humans. In older humans, naïve T-cell populations are extremely small, have impaired homing receptors, a restricted diversity, and shortened telomeres in comparison to young controls. They are therefore unlikely to guarantee full immunological protection following exposure to neoantigens. This defect can be offset, at least in part, by an increasing number of memory T cells, and, in particular, by a subset within this population that constitutively expresses CD25, but is distinct from classical Tregs. This population is diverse and has good proliferative potential, as indicated by its long telomeres as well as by in vitro expansion studies. R. B. Effros (University of California, Los Angeles) pointed out that several clinical studies have shown a correlation between poor antibody responses to influenza vaccination and high proportions of CD8+ T cells with features of replicative senescence. Telomerase-based approaches to reverse replicative senescence were summarized, with data showing that gene transduction with the catalytic component of telomerase (hTERT), or exposure of CD8+ T cells to chemical telomerase activators, results in upregulation of telomerase activity, telomere length stabilization, and enhanced antiviral functions. These in vitro findings may lead to novel strategies to improve vaccine responses in elderly people.

TOR Regulation of Nutrient Sensing

Chair: Matt Kaeberlein, University of Washington, Seattle

The target of rapamycin (TOR) kinase is an evolutionarily-conserved gatekeeper that modulates growth and longevity in response to nutrient availability. When nutrients are abundant, TOR activity is elevated; when nutrients become limiting, TOR activity is reduced. Moreover, mutations that reduce TOR activity increase life span in yeast, worms, and flies. M. Kaeberlein (University of Washington, Seattle) discussed data from comparative genomic studies in yeast and worms that suggest that regulation of mRNA translation is a key mechanism by which TOR activity can influence aging in these organisms. He showed that, compared to randomly selected yeast genes, orthologs of worm aging genes are much more likely to determine replicative life

span, and that many of these longevity-determining ortholog pairs map to the TOR pathway. This set of conserved longevity genes includes TOR itself, ribosomal S6 kinase, translation initiation factors, and ribosomal proteins. Kaeberlein also discussed epistasis studies, supporting the idea that caloric restriction (CR) increases life span via reduced TOR signaling, in a genetic pathway containing S6 kinase and ribosomal proteins. P. Kapahi (Buck Institute for Age Research, Novato, California) stressed the importance of translational regulation by TOR in modulating the longevity of flies. He had previously shown that a reduction in TOR or S6 kinase activity is sufficient to increase the life span of flies. Recent data links the regulation of translation initiation by TOR to CR. Although CR results in a global decrease in translation, a subset of genes is translated at a relatively higher level in CR flies, consistent with the hypothesis that these genes may mediate the longevity benefits.

M. Hansen (Burnham Institute for Medical Research, La Jolla, California) argued that, in addition to regulation of translation, repression of autophagy is an important mechanism by which TOR signaling influences aging. She showed that CR and inhibition of the TOR pathway induce autophagy in *C. elegans*, and that this induction of autophagy is required for the associated life-span extension. Autophagy has been previously reported to be essential for life-span extension in response to reduced insulin/IGF-1-like signaling in worms. Interestingly, Hansen's research has also shown that autophagy is not required for all long-lived *C. elegans* mutants to live long, including mutants with reduced protein translation. Taken together, these observations suggest that autophagy may be required specifically for longevity pathways that are regulated by environmental signals that reflect the availability of food, such as the response to CR and the insulin/IGF-1 pathway. R. Anderson (University of Wisconsin, Madison) discussed the importance of TOR in the response to CR in rodent models. She reported that TOR protein levels increase in adipose tissue of mice subjected to CR. Although induction of TOR by CR is counter-intuitive, Anderson proposed that TOR signaling may be regulated in a tissue-specific manner in mammals, and that the effects of CR on TOR may be different in adipose compared to other tissue types. She also showed evidence that pharmacological inhibition of TOR alters mitochondrial function in mammalian cells and leads to increased sensitivity to oxidative stress. Among the participants, there was consensus that TOR signaling is likely to be involved at a fundamental level in the response to CR, and that multiple outputs of TOR signaling contribute to its effects on longevity.

Comparative Gerontology

Chair: Steve Austad, University of Texas Health Science Center, San Antonio

This symposium summarized and synthesized recent findings relevant to the biology of aging from a comparative perspective. D. Holmes (Washington State University, Pullman) emphasized that birds are valuable, underdeveloped alternatives to classical animal models in the biology of aging, because many bird species are exceptionally long-lived for their body size and lifetime energy expenditure. Clinical biomarkers relating to immunity, oxidative stress, and telomeres may provide data that can be used to examine evolutionary hypotheses about tradeoffs between development, reproduction, and long-term somatic maintenance. Holmes also emphasized the utility of the avian egg in exploring the effects of ''prenatal programming'' on development, reproduction, and somatic health via the manipulation of brood size, yolk androgens, or antioxidants. For example, zebra finches that undergo development in experimentally reduced broods have been shown to reproduce earlier, live longer, and resist some forms of oxidative stress better than those reared in larger broods. R. Buffenstein (University of Texas Health Science Center, San Antonio) presented evidence that naked mole-rats, the longest-lived rodent known (maximum longevity in captivity of 28+ years), exhibit many signs of negligible senescence. For example, they show no evidence of age-related change in reproductive and physiological function, nor is there an observable age-related increase in mortality rate. Although similar in body size to laboratory mice, naked mole-rat females show no decline in fertility between the ages of 2 and 27 years of age. Furthermore, their cells show remarkable resistance to oxidative and genotoxic insults, and necropsy data on several hundred individuals show no evidence of spontaneous neoplasia.

V. Gorbunova (University of Rochester, New York) described her studies on 17 rodent species to analyze telomere length and telomerase activity regulation as a function of life span. She and her colleagues found that neither telomere length nor telomerase activity correlated with life span but, surprisingly, that telomerase activity did correlate with body size. Larger rodents repress telomerase activity in somatic cells; smaller rodents do not, irrespective of longevity. In vitro analysis of primary fibroblasts from these species reveals that cells from large rodents lacking telomerase activity entered senescence, that cells of short-lived telomerase-positive rodents grew rapidly in culture, and that fibroblasts from long-lived telomerase-positive rodents (grey squirrel and naked mole-rat) grew very slowly and did not enter senescence. Genome stability studies suggested that the cells of long-lived species have more stable karyotypes in culture compared with the cells from short-lived species. A. Lambert (Cambridge University, U.K.) reported on his investigation of rates of hydrogen peroxide production by heart mitochondria isolated from mammals and birds with a range of different maximum life spans. During succinate oxidation, maximum life span was observed to be negatively correlated with hydrogen peroxide production at complex I, via reverse electron transport. Statistical analysis of residual maximum life span and residual hydrogen peroxide production revealed that this correlation was even more significant after correction for effects of body mass. These findings indicate that enhanced longevity may be causally associated with low mitochondrial free radical production by mitochondria across species over two classes of vertebrate homeotherms.

Stochastic and Epigenetic Effects on Aging

Chair: Tom Johnson, University of Colorado, Boulder

This session focused on nongenetic differences among individuals, emphasizing variation of age-related traits. Individual life spans can vary as much as 20-fold or more among isogenic individuals kept in a uniform environment, underscoring the role of stochastic effects. Moreover, long-term influences on life span can also be caused by variations early in life, even before birth. L. Kozak (Pennington Biomedical Research Center, Baton Rouge, Louisiana) described his work on environmental and genetic aspects of obesity in genetically identical C57BL/6J inbred mice. His data demonstrate that this interindividual variation in body weight is principally determined by the fat content contributed by all white fat depots, via variation in adipocyte hypertrophy. Gene expression studies revealed that the largest difference in expression occurred in the imprinted gene MEST (mesoderm-specific transcript) that controls the level of protein in the endoplasmic reticulum of the adipocyte, and functions as a gatekeeper at the interface between the adipocyte and the blood capillaries to maintain lipid accumulation in a state of positive energy balance. MEST is very highly expressed at 5 days of age, but subsequently diminishes to almost undetectable levels, unless the mouse enters an obesogenic environment, at which time MEST is induced to levels proportional to those established during lactation. S. Melov (Buck Institute for Age Research, Novato, California) presented data on gene expression profiling of approximately 100 individual nematodes across the life span. Although there was a highly significant differential expression of many genes as a function of age, there was a surprising uniformity of gene expression at the organismal level. One potential confounding factor that might have influenced this result was the homogenization of all cell types in the nematode, which may mask tissue-specific differences among individuals in gene expression.

J. Vijg (Buck Institute for Age Research, Novato, California) discussed studies on the role of somatic mutation, which has been implicated as a major cause of both cancer and aging. Using transgenic animals carrying a chromosomally integrated lacZ mutational target gene, he showed that the types of mutations that were seen in aged animals were organ-specific, for example, in mouse heart and liver; many of the accumulated mutations were genome rearrangements. In *Drosophila*, a postmitotic organism, mutations (mostly genome rearrangements) accumulated at a higher rate at higher temperatures and at higher frequencies than in the mouse. Most recently, studies using direct measurement of transcript levels of housekeeping and organ-specific genes in single cells from liver and heart after single-cell, global mRNA amplification suggest increased ''transcriptional noise'' among old cardiomyocytes and hepatocytes, which could potentially reduce organ or tissue function. Next, T. Johnson described his ongoing studies using a reporter strain of the nematode, *C. elegans*, in which the Green Fluorescent Protein (GFP) gene has been linked to the *hsp-16.2* promoter. This reporter was then induced by a brief heat shock, and the GFP level was assessed quantitatively by a fluorescence-activated worm-sorting device. The level of GFP expression was an accurate predictor of subsequent longevity, with the brighter worms living considerably longer than the dim worms. Assessment of functional biomarkers showed that the short-lived worms had biomarkers predicting shorter life spans (e.g., less movement, greater lipofuscin accumulation). There was little difference in fertility, suggesting that frailty differences were not likely to be responsible for an abnormally short life span of the dim individuals.

Screening for Aging Interventions

Chair: Don Ingram, Pennington Biomedical Research Center, Baton Rouge, Louisiana

The possibility that the rate of aging can be modulated was addressed in this symposium, which focused on some of most promising current screening approaches for evaluating aging interventions. R. de Cabo (National Institute on Aging, Baltimore, Maryland) described his use of serum derived from experimental animals subjected to possible anti-aging compounds to determine its effect on the survival of cells subjected to such in vitro stressors as heat or hydrogen peroxide. This approach is based on his earlier studies, which demonstrated that serum from rodents and monkeys subjected to CR did, in fact, provide such protection, and that the effect was induced, in part, by upregulation of cellular stress proteins, such as Hsp70. Through use of robotics and other technology, de Cabo outlined how this model system could be well adapted to a high throughput screen for aging interventions. G. Lithgow (Buck Institute for Age Research, Novarto, California) reported on a high throughput screen using a new fluorescence-activated sorter that has been specifically adapted for *C. elegans*. Initial screens have yielded a few novel compounds that mediated increased survival following heat shock or oxidative (paraquat) stress, including lithium. Additional studies with lithium confirmed its life-span-extending effects, which appeared to act by modulating histone methylation, and chromatin structure.

Sige Zou (National Institute on Aging, Baltimore, Maryland) described efforts to create a high throughput screen for aging interventions using the Mexican fruitfly, *Anastrepha luden*, which offers several advantages over *D. melanogaster*. He showed population cages capable of housing up to 2000 flies for mortality studies, as well as specially designed individual cages used to measure food intake and egg-laying. He also provided preliminary data on behavior of individual flies as captured by a newly developed video system capable of distinguishing and tabulating data on movement, eating, drinking, and egg-laying. Plans are in place to scale up the capabilities of this facility to a ''megascreen'' in which modules of 1 million flies could be assessed using video imaging to quantitate survival. Finally, R. Miller (University of Michigan, Ann Arbor) provided a progress report on the Aging Interventions Testing Program (ITP) sponsored by the National Institute on Aging, which permits investigators to take advantage of a standardized procedure to evaluate putative aging interven-

tions in a genetically heterogeneous population of mice housed under SPF conditions. Of the four agents selected for analysis during the first phase of ITP operation, the only one that significantly increased survival was nordihydroguiaretic acid (NDGA), and then only in males.

Discussant, H. Warner (University of Minnesota, Minneapolis) endorsed the value and progress of the strategies described by all the speakers but recommended the use of additional animal models, such as short-lived primates, for future screens. R. Strong (University of Texas Health Science Center, San Antonio), the second Discussant, commented on several issues to consider when interpreting differences in survival times between the three ITP study sites. For example, differences in maternal and postweaning diets, specifically protein levels, as well as stress experienced *in utero*, could potentially impact survival. Thus, standardization of all husbandry issues is paramount in studies aimed at evaluating aging interventions.

Parkinson's Disease (PD)

Chair: Marie-Francoise Chesselet, David Geffen School of Medicine at UCLA, Los Angeles, California

New concepts in the mechanisms and etiology of PD, emerging from a wide range of complementary scientific approaches, were discussed in this symposium. W. Langston (Parkinson Institute, Sunnyvale, California) explained that the traditional view of PD primarily as a disease of nigrostriatal dopaminergic neurons must be altered, based on recent pathological findings of accumulation of the protein alpha-synuclein (a cause of rare forms of familial PD) in many neuronal populations throughout the brain and peripheral nervous system. Compatible with the notion that extranigral pathology occurs very early in the development of the disease, he presented evidence that several nonmotor symptoms of PD, for example, sleep disorders and olfactory deficits, frequently precede the onset of classical neurological symptoms. The new view of PD as a generalized disorder affecting many body functions has implications for the way the disease is modeled in animals for studying disease pathophysiology and for developing new therapies. This new paradigm was illustrated by M.-F. Chesselet, who presented her work on genetically engineered mouse models of PD. In contrast to traditional toxin-induced models, mice that over-express alpha-synuclein under a promoter broadly expressed in neurons, Thy-1, not only develop progressive motor anomalies but also exhibit deficits in olfaction, autonomic and digestive function, and anomalies in their circadian rhythm. This constellation of symptoms, which is reminiscent of the early stages of PD, provides useful endpoints for testing disease-modifying therapies.

Another strategy for treating PD is the transplantation of stem cells, or the coaching of endogenous stem cells to replaced lost neurons. However, the success of this approach is predicated on a better understanding of the milieu in which these cells will need to differentiate and survive in an adult, diseased brain. T. Palmer (Stanford University, California) presented his work on the role of inflammation on adult neurogenesis and on the survival of transplanted stem cells. He showed, for example, that antiinflammatory treatment improves the survival of newly generated neurons after stroke, and that endogenous increases in transforming growth factor (TGF)-beta-1 from astrocytes dramatically decreases the generation of new neurons in aged transgenic mice. These findings may be particularly relevant for PD, in light of the epidemiological findings presented by B. Ritz (University of California, Los Angeles). She showed data from a case-control study conducted in rural California populations, which identified new onset PD patients over a 10-year period (1998–2007). UCLA movement disorder specialists examined and evaluated eligible PD patients, and population controls selected from residential parcel maps and initially also from Medicare databases were also enrolled in the study. Blood or buccal cell specimens were collected for DNA extraction, and all participants were interviewed in depth about putative risk factors for PD. There was a greater than two-fold increased risk of PD among carriers of polymorphisms in the TNFα or the IL-1β proinflammatory cytokine genes that have been shown to increase cytokine protein expression, and a nearly three-fold increased risk among carriers of the homozygous variant genotype for either or both polymorphisms. In addition, she found that NSAIDs (nonsteroidal antiinflammatory drugs) play a protective role in PD. These two separate but converging lines of evidence support a role for neuroinflammation in PD.

The Use and Misuse of Science: Hormesis and Homeopathy

Chair: Roger McCarter, The Pennsylvania State University, State College

Two longstanding, but controversial, concepts and their application to health and longevity were discussed in this symposium. The first, hormesis, suggests that long-term exposure to low-level stresses may have beneficial consequences for maintenance of health and extended longevity. Evidence indicates that this may occur by mobilizing cellular defense mechanisms that promote resistance to stress and slow aging processes. The second, homeopathy, involves application of naturalistic methods to healing, but the scientific basis remains unclear.

E. Masoro (The University of Texas Health Science Center, San Antonio) focused on mechanisms underlying the extension of life induced in rodents by the restriction of food (or calorie restriction, CR). Many possible mechanisms of CR have been discussed over the past years, but what is needed is a unifying hypothesis. One such hypothesis is that of ''hormesis,'' or the beneficial cellular effects (such as upregulated maintenance and repair processes) resulting from exposure to mild, repeated stress. A possible model system involving the insulin, IGF-1, glucocorticord, and other metabolic pathways was presented. However, Dr. Masoro emphasized the difficulties involved in testing the global effects expected on the basis of the hormesis hypothesis, given the multiple metabolic pathways involved. H. Brown-Borg (University of North Dakota, Grand Forks) continued this discussion of the involvement of

resistance to stress in mechanisms of aging by describing her studies of long-lived Ames dwarf mice. These diminutive mice exhibit decreased levels of growth hormone (GH), prolactin, and thyrotropin, as well as delayed puberty, but have enhanced antioxidant defenses. Her studies suggest the glutathione (GSH) system may play a major role in enhanced resistance to stress in these mice. In particular, components of methionine (MET) metabolic pathways are upregulated in Ames mice, whereas administration of GH was shown to downregulate several enzymes in the GSH and MET pathways. Her results indicate that differences in pathways of growth and metabolism may be associated with differences in resistance to stress and in longevity.

G. Weissman (New York University, New York) addressed the issue of ''Homeopathy and Kindred Delusions,'' underscoring the absence of the requisite scientific rigor in evaluating claims and techniques of homeopathic medicine. He pointed out that, more than a century after uric acid crystals were shown to be the cause of gout, and that *M. tuberculosis* (TB) is the ''poison'' of scrofula, homeopaths still believe that a vital force of nature is at the root of gout and TB. Indeed, they treat patients having these conditions with homeopathic solutions that involve such extensive dilutions ($1{:}100^{200}$!) as to contain nothing other than solvent. A review of the literature provides no evidence that homeopathy effectively treats physical, as opposed to virtual, disease. Nevertheless, Dr. Weissman emphasized the absence of experimental evidence supporting homeopathic treatments has not deterred the U.S. Federal Government and, indeed, the British Royal Family (Prince Charles) from supporting this practice.

HIV and Aging

Chair: Michael Saag, University of Alabama, Birmingham

Older individuals with HIV represent the fastest rising group of patients with HIV, in large part owing to the remarkable success of antiretroviral therapy and an increased understanding of the pathogenesis of HIV. The risk of newly acquired infection among old individuals is also increasing. A. Justice (Yale University; VA Connecticut Health Care System) reviewed some of these demographic trends, emphasizing that up to 30% of HIV-1-infected persons in the U.S. are undiagnosed and unaware of their infection, and, importantly, a substantial portion of these individuals are over age 40. The median age in the patient population that she and her team follow in the Veterans Aging Cohort Study (VACS) is approximately 50 years (10 years older than the national average) and the majority of veterans in the study are black; nearly all are male. Her research has also shown that older HIV-infected veterans are more likely to have active substance abuse problems, and are also more likely than HIV-uninfected veterans to have multiple health conditions spanning substance use, psychiatric disease, and medical disease. There is also increased concern regarding the higher incidence of cardiovascular disease, liver disease, and cirrhosis due to co-infection with Hepatitis C virus. M. Saag discussed the effects of the revolutionized HIV treatment on the demographics of the disease. With over 25 new antiretroviral agents now on the market, many of which are better tolerated, together with the greater ease of administration (several regimens amounting to 1 to 3 pills per day), the proportion of patients able to achieve undetectable levels of virus in their bloodstream has increased dramatically. In his own clinic, the proportion of patients with undetectable (<50 copies of HIV per milliliter) viral levels has increased from 43% in 2006 to more than 65% in 2007. It is likely that the majority of these individuals will live a relatively normal life span, meaning that the population of aging patients with HIV will increase dramatically over the next decade.

Because HIV disease has major effects on the immune system, a critical question is how these changes interact, or synergize, with normal immunological aging. Research performed by B. Jamieson (University of California, Los Angeles) demonstrates that both age and HIV infection result in a decreased number of naïve helper T cells, which can negatively affect the immune response to neoantigens. The mechanisms responsible for this decrease include infection of these cells by HIV, destruction of the infected cells by the immune system, apoptosis, and increased recruitment of naïve cells into the effector-memory pool. Repeated antigen stimulation of effector-memory cells ultimately leads to senescent T cells that are unable to proliferate, are resistant to apoptosis, have shortened telomeres, and no longer express the CD28 costimulatory receptor. Cells with these features, which accumulate in older persons and in accelerated fashion in persons infected with HIV-1, are correlated with decreased responses to vaccination. A final critical issue, discussed by D. Vance (University of Alabama, Birmingham), was the overlapping effects of HIV and aging on cognitive function, which can involve executive functioning and psychomotor speed. Medications taken by many older patients to treat diabetes, hypercholesterolemia, heart disease, and liver disease can also have effects on cognition. His cross-sectional study on 201 participants, evaluating psychosocial, neuropsychological, and everyday functioning batteries, showed that older HIV-1-infected individuals performed worse on neurocognitive testing for psychomotor skills and executive decision functioning. Thus, cognitive functioning in older adults with HIV disease is likely to impact everyday functioning and the quality of life of these individuals.

Aging Biology for Non-Biologists: Telomeres and Telomerase

Chair: Vicki Lundblad, Salk Institute, San Diego, California

This symposium was intended to introduce GSA meeting attendees to an area of biology that is highly relevant to multiple aspects of aging. The session began with an overview by V. Lundblad, who gave a historical perspective on the field, beginning with the observations of B. McClintock on the unusual nature of the ends of chromosomes in maize, leading to the ''end replication problem,'' which predicted that chromosomal ends would shorten with

each round of DNA replication, and, finally, to the identification of the actual telomere structure and the discovery of telomerase by E. Blackburn and C. Greider. E. Epel (University of California, San Francisco) then discussed the relationship between psychological stress and lymphocyte telomere length. Her studies showed that the perception of stress in women who were caregivers of chronically ill children was associated with shorter telomeres. Telomere shortening is also seen in a variety of age-related pathologies, such as coronary artery disease, diabetes, Alzheimer's disease, and rheumatoid arthritis. Possible underlying mechanisms that are being investigated are oxidative stress and altered balance between cortisol and anabolic hormones. The possibility of manipulating telomeres and telomerase was discussed by C. Harley (Geron Corporation, Menlo Park, California). He described cell-based screens, in which novel telomerase activators and inhibitors were identified for potential use in tissue regeneration and cancer therapy, respectively. TAT2 is a telomerase activator that has hormone-like activity in that its effect is seen at low (nanomolar) concentrations. Direct inhibition of telomerase was mediated by another agent, which is currently being tested in Phase I and II clinical trials for use in such cancers as chronic lymphocytic leukemia and advanced solid malignancies. S. Fauce (University of California, Los Angeles) described studies showing a variety of TAT2 effects on CD8+ T lymphocytes isolated from persons infected with HIV-1. His data demonstrate that short-term exposure to TAT2 increases telomerase activity by as much as seven-fold, enhances production of several relevant cytokines and chemokines, and augments the ability of the T cells to limit HIV-1 production by infected CD4 T cells. The general message from this symposium was that pharmacological manipulation of telomerase (either inhibition or activation) may lead to novel therapeutic approaches to enhance health span in older persons.

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