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Supplementary Materials for

The Demographic and Biomedical Case for Late-Life Interventions in Aging

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Supporting Online Material

Age Changes Targeted for Intervention

Loss of Proliferative Homeostasis: embraces age-related hyperplasia (including excessive proliferation of osteoclasts, interstitial fibrosis, and, above all, cancer), loss of tissue renewal through stem cell attrition [due, e.g., to cellular senescence, apoptosis (1)] or atrophy {from systemic endocrinological and signaling changes [e.g., (2)]}, as well as aberrant differentiation (e.g., accumulation of mesenchymal adipocyte-like cells in aged tissues, incomplete myocyte development in skeletal muscle, osteoblast-like differentiation of calcifying vascular smooth muscle cells, adipogenic transformation of thymic stromal cells in thymic involution, etc).

Neurodegeneration: including but not limited to age-related neurological diseases such as Parkinson's and Alzheimer's diseases, as well as aging changes not normally classified as specific diseases: neuronal loss, synaptic atrophy, loss of synaptic plasticity, loss of interneuronal and intracerebral connectivity, dendritic spine pathology, simplification of neuronal cell geometry, age-related peripheral and autonomic neuropathy, and (arguably) cerebrovascular lipohyalinosis.

Somatic Mutations: occur with aging in both nuclear and mitochondrial DNA. Somatic nuclear mutations are essential to age-related cancers and possibly other age-related dysfunction; mitochondrial mutations (especially deletions) accumulate with aging in postmitotic cells, and appear to contribute to age-related disease (Parkinson's disease, sarcopenia, possibly type II diabetes and congestive heart failure) and rising oxidative stress (3, 4). Other mitochondrial structural and functional alterations also appear to

occur, although cause and effect, adaption vs. dysfunction, functional importance, and other uncertainties remain (5).

Nonadaptive Changes in Gene Expression: increasing variability in gene expression with aging that does not support homeostasis in a changed local or systemic milieu. Includes epimutations and epigenetic drift (6), which may be initially adaptive, by allowing for metabolic flexibility or adaptability, but become progressively deleterious.

Immunosenescence: age-related reductions in adaptive (and possibly humoral) immunity, and alterations in innate immunity associated with thymic involution and alterations in T-cells (7); also heretofore little-understood increases in autoantibodies and alterations in innate immunity (8). Immunosenescence underlies the dramatic increase in morbidity and mortality from infectious disease with age.

Nonadaptive Inflammation: elevations in inflammatory cytokines (notably interleukin-6) and acute-phase reactants (especially C-reactive protein) occur, associated with several age-related diseases, increased frailty, and mortality (9). While anti-inflammatory therapies may prove useful, research should center on developing therapies for the primary cause(s), such as impaired cell-mediated immunity, persistent pathogen infection, oxidative stress, imperfectly-healed injuries, accumulation of senescent cells and adipose tissue macrophages (ATMs) (10), age-related autoimmunity, and possibly impaired target-cell response.

Alterations of the Extracellular Milieu: include thickening of basement membranes, degradation of tight junctions, accumulation of amyloids, crosslinking of long-lived structural proteins by advanced glycation endproducts (AGE), proteoglycan alterations, degradation of tissue elastin structure (11), and mechanical/structural breakdown (12).

May include chronic shifts in signaling milieu, although these are expected to be secondary to primary age changes and revert upon remediation.

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