Cancer & Accelerated Aging ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

# Strategies to Prevent or Remediate Cancer- and Treatment-Associated Aging

## Questions to Guide/Prompt Think Tank Deliberations

| OVERARCHING CRITICAL QUESTIONS |
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| 1) What are the major research gaps for interventions related to cancer and aging? |
| 2) What are the promising solutions to address accelerated aging? Which interventions, if any, are ready for implementation into clinical practice and/or survivorship studies now? |
| 3) Can existing interventions be modified to address the needs of the cancer survivor before, during, and after treatment? |
| 4) Are there interventions being used clinically in other disease states with observed accelerated aging (e.g. HIV)? What are the mechanisms (i.e. hallmarks of aging) through which the interventions prevent/mitigate aging, and can these interventions be adapted to cancer survivors? |
| 5) What efforts are needed to deploy promising interventions into the clinic (implementation science, cost-benefit analyses)? |
| ANIMAL MODELS WITH PROMISING TRANSLATIONAL APPLICATION |
| 6) What are the most promising interventions to attenuate the effects of accelerated aging in animal models? What mechanisms did these models work through/target (e.g. inflammatory processes, increased physical functioning)? Have attempts been made to translate to humans? |
| 7) Can we leverage approaches to understand and modulate cellular senescence and DNA damage repair mechanisms to improve detection or treatment of cancers in older patients? |
| 8) Can alternative models (i.e., organoids) be developed or employed to better understand/interrogate pathways of accelerated aging? Are these models scalable to allow high-throughput screening/analysis? |
| 9) How does accelerated aging (survivorship) differ among pediatric, young adult/adolescent, or adult patient populations, and can these be modeled in mice or other model systems? |
| 10) Do phenotypes of accelerated aging at the cellular level correlate with those at the tissue and whole-organism level? Can model systems be developed that predict at-risk patient populations? |

| EXERCISE INTERVENTIONS |
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| 11) Although we know that exercise interventions are beneficial across multiple populations (including older adults), what are the key considerations for designing, implementing, and sustaining improvements in physical activity among cancer patients and survivors? |
| 12) Have any interventions targeted fatigue as a barrier to exercise interventions? Are there tailored exercise programs by cancer and treatment type? |
| 13) Has exercise, or any of these interventions for that matter, been shown to reverse/favorably change the hallmarks of aging to reduce the onset of aging phenotypes in humans, including multimorbidity and functional decline?[1,2] What is the effect of sedentary behavior, and its reduction, on hallmarks of accelerated aging, especially for cancer survivors? |
| 14) Considering that aerobic and resistance exercise convey differential as well as synergistic benefits generally toward health, are there differential or synergistic effects of resistance exercise or aerobic fitness-enhancing exercise that favorably impact accelerated physical aging and/or cognitive function? |
| 15) Are specific exercise prescriptions that refine (i.e. apply FITT principles) the 2018 Physical Activity Guidelines necessary to lessen or prevent accelerated physical and/or cognitive aging? |
| 16) Do physical activity interventions produce different effects on cognitive functioning than those produced by other types of activity, such as playing musical instruments or cards? |
| 17) How can we develop interventions to improve outcomes in patients with functional impairment? |
| NUTRITION INTERVENTIONS |
| 18) What is the beneficial evidence for nutritional intervention among cancer patients? Do interventions help avoid the onset and progression of sarcopenia/cachexia in older cancer patients? |
| 19) Is protein or other nutrient supplementation efficacious in a pre-habilitation and/or rehabilitation setting? |
| 20) Are the current paradigms for pre-chemotherapy diets counterproductive? |
| 21) Are there effective nutrition interventions with the appropriate macronutrient composition to attenuate the effects of aging and reduce cancer risk? |
| 22) For obese cancer patients, can weight loss before or during chemotherapy reduce toxicities and improve cancer treatment efficacy? |
| 23) Can interventions be developed and tailored for older adults with cancer? |
| COGNITIVE INTERVENTIONS |
| *Note: Almost all of the studies examining interventions for cognitive decline are small, typically underpowered trials. Therefore, there is not much knowledge base for selecting interventions.* |
| 24) Should interventions target cognition, take a more systemic approach (e.g. exercise), include components that target fatigue and psychological factors (depression and anxiety), or all of the above (i.e., multicomponent interventions)? |

25) Part of the difficulty in developing interventions is related to the lack of understanding of which cognitive domains are affected by cancer treatments. Survivors all report memory problems, but typically perform normally on neuropsychological tests of memory. Newer research, based on methods from cognitive neuroscience, suggest that attentional processes (including pre-attentive processing), inability to filter out irrelevant information, and slowing of processing speed are most affected – all of which could impact memory because information is not stored properly. These data point to interventions that are quite different from traditional cognitive rehabilitation approaches (e.g. interventions that focus on filtering out irrelevant information and increasing processing speed).

26) What are the most relevant outcomes, self-report or performance on cognitive tests (which frequently do not correlate well)?

## SUPPORTIVE CARE INTERVENTIONS (PSYCHOSOCIAL, BEHAVIORAL, INTEGRATIVE MEDICINE)

27) What is known about personality and survivorship in the general cancer population? Is there any literature limited to older adults?

28) What is the strength of the evidence for supportive care interventions? In what setting are they most practical?

29) Are there interventions that could help patients and caregivers who have depression or anxiety?

30) Are there supportive care interventions that could help mediate nutritional problems in older patients with cancer?

31) How does social support relate to treatment practice patterns in older adults with cancer?

32) Can infrastructure be strengthened to address social support issues of older cancer patients?

33) What is the efficacy of using multidisciplinary clinical teams (pharmacy, social work, nursing, care managers or patient navigators) on cancer patient and caregiver endpoints?

## MULTICOMPONENT/TRANSLATIONAL INTERVENTIONS

34) What types of patients/survivors are best to recruit for interventions (e.g. age, cancer type/stage, treatment)? How do we account for rapidly changing treatment options in analyses? For example, it is difficult to discern the benefits of an intervention if treatment options vary widely across the population. Moreover, treatment options are rapidly evolving, making it very difficult to define a target population.

35) What combinations of interventions are most appropriate for cancer survivors across the cancer control continuum? Which are most efficacious?

36) Is there a practical toolbox that cancer survivors can be given to incorporate efficacious interventions in daily life? What about leveraging mHealth or eHealth? Are they successful?

37) How can we translate efficacious interventions into better models of care?

## MEASUREMENT/DESIGN CONSIDERATIONS

38) Should we be recommending proof of concept trials as a feasible way to establish preliminary evidence?

*(References on back)*

**References**

1. Figueira I, Fernandes A, Mladenovic Djordjevic A, et al. Interventions for age-related diseases: Shifting the paradigm. *Mech Ageing Dev.* 2016; 160: 69–92.
2. Hastings WJ, Shalev I, Belsky DW. Translating Measures of Biological Aging to Test Effectiveness of Geroprotective Interventions: What Can We Learn from Research on Telomeres? *Front Genet.* 2017; 8:164.