Cancer & Accelerated Aging ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

Think Tank #1: Measuring Aging And Identifying Aging Phenotypes In Cancer Survivors

Compilation of Critical Questions Related to Accelerated Aging Among Cancer Survivors

	Identifying "aging phenotypes" and understanding the trajectory(ies) of aging among cancer survivors
1	What does a healthy life span look like after exposure to cancer treatments? How is health span regarded in a cancer survivorship context?
2	Does the increased prevalence in age-related comorbidities, higher inflammatory profiles, etc., in cancer survivors, compared with age-matched cancer-free individuals, represent premature ("accelerated") aging, or does it reflect specific outcomes related to cancer diagnosis and treatment toxicity, and/or side effects?
	a. Is it possible to elucidate unique "hallmarks of aging" within the context of cancer survivorship? Can this be a manuscript goal?
	b. Are we essentially interested in secondary aging? Do cancer and cancer treatment result in "injuries to the organism that cause aging" or a change in the rate of aging? Can secondary malignancies be thought of as a secondary aging outcome (Ng et al., 2010)?
	c. Is the dual process model of aging proposed by Busse (1969) considered a valid theory, or has it been debunked or replaced by a contemporary perspective?
3	What are the aging phenotypes in the general population (NIA input)?
4	Are the mechanisms by which treatments/cancer diagnosis are associated with age-related phenotypes consistent with the known "hallmarks of aging"?
	a. If yes, is aging "accelerated" or "accentuated (phase shift)"? What is the aging trajectory for cancer survivors? How do the newer cancer therapies (immunotherapies) affect the aging trajectory?
5	How do we best measure aging?
	a. The issue of measuring aging is a thorny one, and the simple answer is: No, we don't have proper measures at this moment. One of the best measurements we have is the epigenetic clock, and that has been applied to cancer patients, but the results are not fully convincing (the slope is not changed, but it's a rather rough measurement and it needs to be repeated with additional tools). There's also the attempts by Belsky to measure physiological aging based on an algorithm derived from NHANES, but again, this requires further confirmation.
	Mechanisms by which cancer/cancer treatment lead to accelerated aging (or aging phenotypes)
6	What mechanisms lead to accelerated aging?
	a. Recognizing that animal models (typically young-aged animals) are extensively utilized to phenocopy human cancers and test therapeutic approaches, do animal models accurately reflect the accelerated aging observed in humans? Can these models be improved to better understand and investigate accelerated aging pathways and develop novel interventions to stabilize or reverse aging processes?
7	How do aging processes influence cancer biology and progression?
8	How do aging and cancer processes interact in the inflammation/coagulation pathways?

9	How do cancer treatments impact aging? How can cancer and cancer treatment be used to further our understanding of the molecular pillars of aging?
	a. Are the primary targets of these drugs leading to accelerated aging?
	b. Are the side effects of these drugs leading to accelerated aging?
	c. Many of these drugs lead to apoptosis in the targeted cell. Is it possible that there are too many apoptotic bodies for the system to remove, and these produce aging effects? It might be worthwhile to consider the antibody-targeted therapeutics whose cytotoxic portions are delivered to the tumor or metastatic cells. These might be expected to have the lowest acceleration effect on aging because they do not reach off-target cells (or not at high frequency if they work as designed). Alternatively, that targeting might not matter if the outcome is the same as that of less-targeted therapies. For example, many of these drugs lead to cell death (possibly apoptosis, but there are many forms of cell death, each with its own consequences for neighboring cells). Apoptosis, at least, is a feature of aging (as well as development) – but the point is that killing cancer cells might leave around more corpses than can be handled or that might release more factors from cell death that affect other cells, and those might accelerate aging. Biologically, it seems that the living need to cope with their dead neighbors – something of a cellular social network for coping with stress: maybe there is just too much stress (or something like that).
	d. How do therapy-induced senescent cells contribute to age-related consequences of cancer treatment exposure?
	e. Which senescence-related chemotherapy side effects are due to SASP-induced immune activation? Which immune components?
	f. Which senescence-related chemotherapy side effects are due to SASP factors independent of the immune system? Which factors?
	g. Does getting cancer treatment during a specific life stage (e.g., puberty, pregnancy, or menopause) lead to increased toxicity or disrupt natural aging/development?
10	How much of the distal damage caused by tumors is due to tumor-induced immune activation? Which components?
	Early Diagnosis and Surveillance of Accelerated Aging
11	What treatment toxicity profiles can be used as early warning signs for loss of function over time?
12	Can a panel of clinical/biological tests be used to identify and monitor progression to “aging phenotypes” in cancer survivors?
13	Can the Tipping Point Theory be used to describe aging among cancer survivors? If so, what is the tipping point, and what are the pre-symptomatic early warning signs?
14	Can we measure the loss of resilience earlier in adulthood, before the occurrence of frailty?
	a. One potentially novel approach being tested is measurement of resilience of cells in culture. Basically, the idea is to test in a patient’s cells how they respond to a challenge such as chemotherapy. If it pans out, this could become a simple test to predict responsiveness to treatment, side effects, etc. The thinking is that a cell in culture might (or might not) capture the exposome of the individual, but at the least, it should capture the genomic influences in the trait.
	Risk and Protective Factors
15	What risk factors result in a temporary setback or a continual decline? What changes are protective? Are the changes reversible?
	a. What are the risk factors that lead to prefrail/frail states in older adults and that are predictive in younger individuals? From a dynamic systems perspective, system slowing, slow recovery from a system challenge, and increased variability are predictors of critical transitions. Reduced time in the get-up-and-go task is predictive. Other potential tests might be increased heart rate variability, time to return to resting heart rate following exercise, glucose challenge, and dexamethasone suppression.

	b. How do we protect physiological/functional reserve, protect against chronic multiple organ dysfunction, and preserve healthy life span?
	c. Who benefits, who does not? Are there "exceptional responders," individuals/groups whose measures of aging aren't accelerated after cancer therapy? Can these individuals/groups be identified and studied? If so, this could represent a toehold to better understand accelerated aging.
	d. Do accelerated aging trajectories differ by cancer treatment, cancer population/age group, etc.?
	e. Is there a differential impact on the rate of aging that depends more on the type and stage of the cancer and less on the therapy? That would be complicated by the range of targets, meaning that it might be the case that one class of molecules is targeted for therapy in one class of cancers — so it would be hard to distinguish target effects from cancer effects.
	f. Are the effects additive, multiplicative, synergistic?
16	Do high global pro-senescence stress and a compromised immune system lead to accelerated aging?
17	Do certain cancer treatments increase survivors' vulnerability to multiple diseases? How does this intersect with aging, which also increases vulnerability to multiple diseases?
18	What are the best biomarkers, cellular and molecular characteristics that predict or protect from age-related consequences of cancer treatment exposure?
	a. Consider the contributions of the patient's health (psychosocial, physical, and physiological) and lifestyle (e.g., smoking, obesity, sedentary behavior) prior to diagnosis, during treatment, and after treatment on the rate of aging among cancer survivors.
	Solutions/Interventions to Prevent or Mitigate Accelerate Aging
19	Can we intervene to slow down (mitigate) or reverse accelerated aging? What can we speculate based on current knowledge?
	a. What interventions will restore baseline function or slow functional decline?
	b. Are there interventions we can do now that might work? How responsive are survivors to interventions that impact aging?
	c. Do interventions need to be personalized (Lee Jones-physical activity)? Interventions logically must work through the biological mechanisms by which treatments/cancer diagnosis cause premature aging.
	d. What is the role of "pre-habilitation?"
20	Can we establish direct experimental evidence that cancer-related inflammatory/coagulation factors produce organ damage, and whether there are common mediators across organ systems or unique ones for each?
21	Are inflammation/coagulation pathways targetable to improve function and survivorship as people age?
	Considerations for Designing Future Accelerated Aging Studies
22	How can we study the mechanisms that lead to accelerated aging?
23	How do we obtain experimental evidence?
24	How do the elderly fare in terms of morbidity and mortality in treatment clinical trials? Most clinical trials are based on data from younger cohorts with near-perfect lung, heart, liver, and kidney function. A large clinical trial is needed to examine the impact of reduced/modified starting or later cycle treatment on survival and morbidity.
25	Can the geriatric assessment be used to create more liberal eligibility criteria for clinical trials?
26	Who is the ideal population to study? It is important to understand biological processes (and the host genetics that underlie differential responses to the potential cancer and treatment insult) responsible for aging phenotypes so we can target interventions and perhaps have some easy biomarkers that will allow us to screen for those who are most at risk. As childhood cancer survivors (particularly those treated in early childhood) don't start out with the same life exposures (smoking, sedentary behavior, years of poor diet) as older adults, they don't come into therapy with a ton of crazy co-morbidities that affect their response/outcomes. They may be an informative population for biology studies.

	a. Even though survivors of childhood cancer had not all been exposed to all the deleterious (and some positive) elements of life when the therapy was applied, we also need to keep in mind that, if we're talking of accelerating aging, the ultimate phenotype is still affected by lifestyle, even if that lifestyle occurs after the initial insult.
	Datasets
27	Are there existing studies (or "banks" of information) that could serve as the infrastructure to measuring aging-related phenotypes longitudinally to investigate aging-related trajectories among cancer survivors?
28	What novel methods can be employed to look at accelerated aging? Looking at system processes? Deep learning of appropriate datasets? Can we leverage datasets such as CancerLinQ?
	Modeling
29	Can risk-prediction models be developed? If so, what do we need to develop models of adverse health outcomes that change the rate of aging? How granular do we need to focus to extrapolate from individual to population-level effects? What is the utility of these risk-prediction models? Should this information be incorporated into clinical decision-making (risk/benefits of certain treatments)?
	a. Resource: Efforts to do this in the UK – see a recent paper in childhood survivors.
	b. Deemed an urgent survivorship priority at ACS
	c. Resource: Salz et al (2015) paper, a MSKCC investigator
30	Can multi-level systems modeling approaches be used to understand what accelerated aging is and what the phenotype looks like beyond the measurement of one biomarker? Can they be used to identify individuals who need intervention and to develop personalized cancer rehabilitation interventions?
31	Which advanced statistical analysis techniques hold potential for understanding how brain structure and function change with aging and in response to insults to the brain caused by cancer and cancer treatments?
32	Which models are most appropriate to use to study how brain structure and function change with age and by cancer treatment?
33	Which models describe the resiliency and failure of complex systems? Which are the most appropriate for guiding research related to the interactions of aging processes, cancer, and cancer treatments in determining cognitive aging?