Cancer and the Aging Body

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No Disclosures

I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.
Multiple Hit-Induced Multisystem Toxicity

Baseline risk factors
SMOKING, HYPERTENSION, AGE

‘Direct’ hit
CANCER / SURGERY / THERAPY

‘Indirect’ hit
SECONDARY TO CANCER / SURGERY / THERAPY
(E.G., DECONDITIONING)

CANCER PATIENT

COGNITIVE IMPAIRMENTS
IMMUNE DYSFUNCTION
CARDIAC ATROPHY
ANEMIA
GASTROINTESTINAL EVENTS
EXERCISE INTOLERANCE
SKELETAL MUSCLE ATROPHY
BONE DEMINERALIZATION
Current Assessments

ASSESSMENT ACROSS THE CANCER CONTINUUM

PRE-THERAPY
- PERFORMANCE STATUS, CHRONOLOGICAL AGE
- CARDIAC, PULMONARY FUNCTION

DURING THERAPY
- CARDIAC, PULMONARY FUNCTION

POST-THERAPY
- CARDIAC, PULMONARY FUNCTION

SCOTT ET AL. J CLIN ONCOL, 2020
Current Management

PHARMACOLOGY ACROSS THE CANCER CONTINUUM

PRE-THERAPY

DURING THERAPY

POST-THERAPY

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MSK EXERCISE ONCOLOGY SERVICE
Multisystem Countermeasures Program

PHENOTYPING

- Behavioral / Social (Physical Activity, Diet, Sleep)
- Integrative Function (CRF)
- Organ Networks
- Cellular Networks
- Molecular Networks
- Genes

INTERVENTIONS ACROSS THE CANCER CONTINUUM

- At Diagnosis: To augment reserve
- During Therapy: To mitigate decline
- Post-Therapy: To return to baseline levels
Phenotyping
Integrative: Geriatric Assessment

A Practical Approach to Geriatric Assessment in Oncology

WHAT IS GERIATRIC ASSESSMENT?

- Depression
- Cognition
- Function
- Social Support
- Physical Performance
- Nutrition
- Co-morbidity

FEASIBILITY

- HURRIA ET AL. J CLIN ONCOL, 2011

PROGNOSTICATION

- HURRIA ET AL. J CLIN ONCOL, 2011
- EXTERMANN ET AL. CANCER, 2012

GA-GUIDED CLINICAL CARE

- HURRIA ET AL. J CLIN ONCOL, 2016
- CORRE ET AL. J CLIN ONCOL, 2016

GA-GUIDED INTERVENTIONS

- NADARAJA ET AL. J GERIATR ONCOL, 2020
- DERMAN ET AL. J GERIATR ONCOL, 2021
- LI ET AL. JAMA ONC, 2021
Integrative Physiological Function: Cardiorespiratory Fitness

Cardiopulmonary Exercise Test (CPET)
- Symptom limited cardiopulmonary exercise test
- Cardiorespiratory fitness (VO$_2$peak – mL.kg$^{-1}$.min$^{-1}$)

Therapy-induced accelerated physiological aging

Healthy Aging
10 YEARS

AC
12 WEEKS

BMT
6 WEEKS

HORNSBY ET AL. ACTA ONCOL, 2014
JARDEN ET AL. BMT, 2009
Integrative Physiological Function: Cardiorespiratory Fitness

**STUDY #1: Persistent Impairment**
- Breast cancer (n=140)
- Healthy age-matched (n=107)
- 3 years post-therapy

![20 YEARS AGE DIFFERENCE](image)

**STUDY #2: Prognostic Importance**
- Various Cancers (n=1,632)
- 5-year follow-up

![Hazard Ratio (95% CI)](image)

JONES ET AL. J CLIN ONCOL. 2012
GROARKE ET AL. EUR HEART J QUAL CARE CLIN OUTCOMES, 2020
MSK EXERCISE ONCOLOGY SERVICE
Organ-Level Assessments

**STUDY #1:**

**Cognitive Function**

- Lymphoma (n=248)
- Healthy age-matched (n=212)
- Pre chemotherapy; at chemotherapy completion; 6 mo post chemotherapy

**STUDY #2:**

**Pre-HCT Muscle**

- Leukemia / MDS (n=859)
- 2-year follow-up

**Non-Sarcopenic**

- FACT-Cog Total Score

*Healthy Control* vs *Cancer*

Adjusted HR: 1.4 (1.09-1.78)

-JANELSINS ET AL. J NATL CANCER INST, 2021
-ARMENIAN ET AL. J NATL CANCER INST, 2019*
Blood-Based Biomarkers

**STUDY #1: Inflammatory Markers**
- Breast cancer (n=248)
- Healthy age-matched (n=106)
- Pre chemotherapy; 6 mo post chemotherapy; 18 mo post chemotherapy

**STUDY #2: Clonal Hematopoiesis**
- Adult cancers (n=10,138)
- Cancer therapy exposed (n=5,978)
- Cancer therapy naïve (n=4,160)

**STUDY #3: Clonal Hematopoiesis**
- Non-Hodgkin lymphoma (n=401)
- With CH (n=120)
- Non-CH (n=281)

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ALFANO ET AL. J CLIN ONCOL, 2017
BOLTON ET AL. NAT GENET, 2020
GIBSON ET AL. J CLIN ONCOL, 2017

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MSK EXERCISE ONCOLOGY SERVICE
Summary: Aging Across the Cancer Continuum

Pre Treatment
~ 17% lower

During Treatment
↓ 10%-20%

Acute Post Treatment
~ 30% lower

Chronic Post Treatment
↑ 20%-50% IN EVENTS

High Risk at Diagnosis
↓ Reserve
Interventions
Exercise Training Across the Cancer Continuum

Pre Surgical
↓ ~40%
POST-OP EVENTS RISK

During Treatment
↑ 5%-10%
VO2 PEAK

Acute Post Treatment
↑ 10%-20%
VO2 PEAK

Chronic Post Treatment
↓ 20%-40%
CVD EVENTS RISK

SCOTT ET AL. JAMA ONCOL, 2018
SCOTT ET AL., J CLIN ONCOL. 2018
Cardiac Symptoms

High-dose anthracycline/radiotherapy*

Low-dose anthracycline or trastuzumab + ≥2 RF, or age ≥ 60 yrs

Low-dose anthracycline + trastuzumab

None or other

After exposure, assess symptom/dx

No symptoms/dx

Cardiopulmonary exercise test

CV consult

Cardio-oncology rehabilitation exercise (CORE)

Community-based programs for cancer patients

GILCHRIST ET AL, CIRCULATION, 2019
Randomized Exercise Trial in Chronologically Older Breast Cancer Survivors

**Stretching vs. Resistance and Aerobic Exercise**
- n=114 breast cancer survivors
- >2 years post-therapy
- Mean age: 71 years (64-87 years)

Randomized to 12 months supervised + 6 months unsupervised of:
- STRETCHING CONTROL (N=38)
- RESISTANCE EXERCISE (N=39)
- AEROBIC EXERCISE (N=37)

**Study results**

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<th>BEFORE</th>
<th>AFTER</th>
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<tr>
<td>AEROBIC</td>
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<td>630</td>
<td>480</td>
<td>600</td>
<td>540</td>
<td>590</td>
</tr>
</tbody>
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WINTERS-STONE ET AL., J GERIATR ONCOL, 2021
Randomized Exercise Trial in Phenotypically Older Breast Cancer Survivors

Stretching vs. Linear and Non-Linear Aerobic Exercise

- n=174 breast cancer survivors
- 1-5 years post-therapy
- Mean chronological age: 58 years
- Mean physiological age: 73 years

Randomized to 16 weeks of:

- STRETCHING CONTROL (N=57)
- LINEAR EXERCISE (N=58)
- NON-LINEAR EXERCISE (N=59)

Individual Patient Response

<table>
<thead>
<tr>
<th>Change VO₂peak (mlO₂·kg⁻¹·min⁻¹)</th>
<th>~35% EXERCISE EFFECTIVE</th>
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<tbody>
<tr>
<td></td>
<td>~65% EXERCISE NOT EFFECTIVE</td>
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</table>
Randomized Exercise Trial in Older Lung Cancer Survivors

**Stretching vs. Aerobic, Resistance, and Combined Exercise**
- n=90 lung cancer survivors
- 1-10 years post-therapy
- Mean chronological age: 65 years
- Mean physiological age: >80 years

Randomized to 16 weeks of:
- STRETCHING CONTROL (N=23)
- AEROBIC EXERCISE (N=24)
- RESISTANCE EXERCISE (N=23)
- COMBINED EXERCISE (N=20)

**Individual Patient Response**

![Graph showing change in VO2peak (mL/kg/min⁻¹) for different exercise groups.](image-url)
Randomized Pharmacological Cardioprevention Trial in Breast Cancer

Placebo versus ramipril, bisoprolol, or ramipril plus bisoprolol

- n=174 breast cancer patients
- Initiating anthracyclines +/- trastuzumab
- Mean chronological age: 48 years

Randomized to 1 year of:

PLACEBO CONTROL (N=42)
RAMIPRIL (N=43)
BISOPROLOL (N=45)
RAMIPRIL + BISOPROLOL (N=43)

Study results

LVEF, GLS

Proportion of patients with >10% reduction (%)
Phase I Senolytics Trial in Diabetic Kidney Disease

Dasatinib and Quercetin (D + Q)
- n=9 diabetic kidney disease
- Mean chronological age: 68 years

3 days of oral D 100 mg + Q 1000 mg

Adipose tissue, skin biopsies, and blood collected before and 11 days post-treatment

**Individual Patient Response**

**SIGNIFICANT REDUCTION IN ABDOMINAL SUBCUTANEOUS ADIPOSE TISSUE SENESCENT CELLS**

**SIGNIFICANT REDUCTION IN PLASMA SASP FACTORS**

**fold change**

1 2 3 4 5 6 7 8 9
Future Directions
Spaceflight: Dense and Dynamic Phenotyping

Multidimensional, longitudinal assays of the NASA Twins Study. (Left and middle) Genetically identical twin subjects (ground and flight) were characterized across 10 generalized biomedical modalities before (preflight), during (inflight), and after flight (postflight) for a total of 25 months (circles indicate time points at which data were collected). (Right) Data were integrated to guide biomedical metrics across various “omes” for future missions (concentric circles indicate, from inner to outer, cytokines, proteome, transcriptome, and methylome).

Garrett-Bakelman et al., Science 364, 144 (2019) 12 April 2019
Targeted Intervention Strategies to Optimize Response
Data Driven Approaches

INPUT

DATA INTEGRATION / RISK STRATIFICATION

OUTPUT: INTERVENTIONS

BEHAVIORAL / SOCIAL
(Physical Activity, Diet, Sleep)

INTEGRATIVE FUNCTION
(CRF)

ORGAN NETWORKS

CELLULAR NETWORKS

MOLECULAR NETWORKS

GENES

INTEGRATIVE FUNCTION

(crf)

Development

Blood Biochemistry

Body Composition

Vitamin

Ferritin

Iron

Liver Function

Muscle Strength

Cellular Health

Tumor Growth

Cardiac Function

Dysregulation

Vascular Health

Mitochondrial Health

Immune System

DNA甲基化

RNA甲基化

Protein甲基化

Phenotypes

Genotypes

Risk Factors

Interventions

Input

Data Integration / Risk Stratification

Output: Interventions

Scott et al., Circulation, 2018

MSK EXERCISE ONCOLOGY SERVICE
Digital Phenotyping

**Current Phenotyping: Center-Based**

- Behavioral/Social (Physical activity, diet, sleep)
- Integrative Function (CRF)
- Organ Networks
- Cellular Networks
- Molecular Networks
- Genes

**Next Frontier: Digital Dynamic Phenotyping**

Wearable sensors enable personalized predictions of clinical laboratory measurements.

- Heart rate
- Skin temperature
- EDA
- Steps
- CCA

**Model building**
- Lasso
- Random forest
- CCA

**Model testing**
- Bootstrap
- Leave-one-person-out cross validation
- Variance explained (R)

- Hemoglobin
- Absolute monocyte count
- Hematocrit
- Chloride
- Red blood cells
- Glucose
- Glycated hemoglobin

*Images and diagrams sourced from Dunne et al., Nature Medicine, 2021.*

SCOTT ET AL. J CLIN ONCOL, 2020
DUNN ET AL. NAT. MED, 2021
Digital Interventions
Knowledge Gaps

EPIDEMIOLOGY
- Prognostic importance of biomarkers
- Risk stratification using dense and dynamic phenotyping

PRECLINICAL
- Mechanisms of multi-disease across the lifespan
- Intervention effects in appropriate models

CLINICAL SAFETY / SIGNAL SEEKING
- Phenotype-guided clinical care / interventions
- Individual patient responses

DEFINITIVE PHASE 2/3
- Effects of interventions on hard endpoints
- Multi-site trials

IMPLEMENTATION
- Patient / Clinician uptake
- Cost

- Implementation
- Preclinical
- Clinical Safety / Signal Seeking Trials
- Definitive Phase 2/3 Trials
- Epidemiology
Research Opportunities

**Epidemiology**
- Leverage existing sources (CCSS, CRDC) for ‘systems’ epidemiology

**Preclinical**
- In vitro and in vivo models based on human data
- iPSC, organoids for modeling and interventions

**Clinical Safety / Feasibility**
- Sequential multiple assignment randomized trials (SMART)

**Definitive Phase 2/3**
- Leverage clinical trials networks
- Digitized trials with centralized cores

**Implementation**
- Multiphase optimization strategy (MOST)
Research Gaps

Leverage ongoing trials

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

PAR-21-055:
• Time-sensitive mechanistic ancillary studies to ongoing clinical projects
• Identify novel targets for diagnosis, treatment, and prevention of disease
• Collaboration between basic and clinical investigators
• Collaborations in which a senior investigator from the parent study supports a junior investigator to serve as PI on an ancillary study are encouraged

Standard measures

Optimized, minimal set of core measures:
• Costs of standard measures covered
• Single data repository

Cross-cutting programs

MoTrPAC
The Molecular Transducers of Physical Activity Consortium
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