Project Details	
Project Code	MRCPHS25Ex Revuelta Iniesta
Title	Understanding Muscle Growth Responses to Nutrition in Adult Survivors of Childhood Acute lymphoblastic Leukaemia
Research Theme	Population Health Sciences
Summary	Survivors of childhood acute lymphoblastic leukaemia (ALL) experience premature frailty and muscle atrophy. Muscle protein synthesis is crucial for muscle growth and is mainly stimulated by physical activity and dietary protein. Since dietary protein intakes in ALL survivors do not differ from the general population, it is suggested that the observed muscle atrophy is caused by an inability of muscle growth to respond normally to dietary stimuli, termed anabolic resistance. This PhD will mechanistically explore if anabolic resistance underlies frailty in ALL survivors in response to diet, and design tailored dietary and exercise interventions to promote muscle growth.
Description	Sixty percent childhood Acute Lymphoblastic Leukaemia (ALL) survivors experience frailty 25 years before the general population (44 vs. 69 years) (Smitherman et al. 2020). Frailty, defined as muscle atrophy, exhaustion/low energy expenditure and weakness (Fried et al. 2001), leads to more comorbidities, relapse, and death (Ness et al 2013). Skeletal muscle mass is determined by the balance of protein muscle synthesis (MPS) and breakdown. MPS is stimulated by exercise and dietary protein and is considered a predominant component that dictates muscle growth (Davies et al. 2020). Protein intakes in ALL survivors do not differ from the general population (Belle et al 2017) suggesting an inability of MPS to respond normally to dietary stimuli, termed anabolic resistance. Indeed, anabolic resistance is a primary driver for muscle loss with age and inflammatory conditions. We showed that anabolic resistance may be driving muscle loss in Crohn's disease, which has a similar muscle phenotype to ALL (Davies et al 2021). Studies investigating if anabolic resistance is a pathophysiology mechanism of frailty and dietary strategies designed to ameliorate frailty in ALL survivors are lacking. This project will measure muscle protein balance in childhood ALL survivors and matched-healthy controls in the fasted and fed states together with inflammatory and functional readouts to provide holistic muscle phenotypes. The results will be used by the PhD student to devise and test various nutrition (e.g. protein) or exercise strategies to promote MPS in subsequent studies. **Key research questions** 1. In those with muscle atrophy, is this explained by anabolic resistance of muscle in response to a protein-based drink in childhood ALL survivors when compared to matched healthy controls? 2. Do childhood ALL survivors have higher inflammation than matched healthy controls and is it associated with anabolic resistance? 3. Is higher protein intake associated with an improved forearm muscle protein net balance under fasted and fed conditions in both groups? 4. Can diet and resistance exercise overcome anabolic resistance in childhood ALL survivors?

Specific Objectives and PhD timelines:
Year 1, 9 months: Compare frailty phenotypes (body composition, muscle function and inflammation) in childhood ALL survivors and matched healthy controls.
Year 1, 12 months: Compare forearm muscle protein net balance under fasted and fed conditions in both groups. Explore associations between dietary patterns and inflammation and muscle net balance under fasted and fed conditions.
Year 2 and 3: The student will devise and test various nutrition (e.g. protein) or exercise strategies in similar subsequent studies based on findings from the proposed study described below:
Experimental Approach
Cross-sectional study.
Population
There are 1200 ALL survivors in Southwest England. We will recruit 16 who have been cured for ≥5 years since diagnosis between the ages of 18 – 70 years and 16 age-, sex- and BMI matched healthy controls using social media.
We will exclude pregnant and lactating women and people with metabolic, severe cognitive and relevant allergy and intolerances.
Protocol (Arterialised venous deep blood (AV-V)) (Dirks et al. 2019).
Visit 1 takes 2.5 hours. We will measure body composition (BodPod), skeletal muscle strength, function, and balance, and ask participants to complete a Food Frequency Questionnaire (EPIC-Norfolk) and physical activity (IPAQ). A standard meal will be provided to consume that night.
Visit 2 is the experimental protocol, named AV-V performed in Nutrition Physiology Research Unit by a very experienced research team.
The experiment takes 5 hours structured in minutes as -60, 0 (Ensure Plus, Abbott Nutrition), +60, +120 & +180 min.
Participants will be fasted and asked to rest on a bed for the experiment.
Time -60 min: a 1st cannula will be placed into a dorsal hand vein and then in a heated hand warmer (55°C) for the remainder test day to repeatedly sample AV-V.
Time -60 min: a 2nd cannula will be placed into a deep-lying antecubital arm vein. Ultrasound is used to locate its anatomy, assist in the cannulation and calculate brachial-artery blood flow. These cannulas are kept patent by a continuous saline drip. Oxygen saturation confirms AV-V blood.
Arterialised blood and venous blood samples will be collected at baseline (-15 min) every 15 minutes until +180 minutes (total 11 samples) to analyse insulin, glucose and serum branched chain amino acid concentrations. Brachial arterial blood flow will be assessed concurrently with blood sampling to calculate arteriovenous forearm balance of the measured nutrients. Inflammatory markers will be analysed from baseline samples. Resting and fed energy expenditure will be measured via indirect calorimetry at times – 30, +50 & -170 min.
Power calculation
A 2-sided ANOVA repeated measures power-analysis showed that the project requires 7 participants per group to detect differences in amino acid balance (μmol/min/100g forearm-lean-mass) between groups (α=0.05; 80% power). Two age groups (18 – 39 and 40 – 70) will account

	for the 25 years-age difference in frailty onset requiring 7x4 (28) with 10% drop-out (n = 32).
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