

# قواعد الفهرسة الأنجلو-أمريكية

## ومارك 21

# AACR2 with MARC21

### 1 Introduction

Breast cancer (BC) patients treated with adjuvant chemotherapy, particularly with aromatase inhibitors (AI) containing regimens, often experience a change in body composition, such as increases in lean mass, decreases in total body mass, and a decrease in fat mass, which can impact fatigue, quality of life and physical functioning during treatment and years after treatment has ended. The cause of these treatment-related changes in body composition is unclear. Growing evidence points to an endocrine system, and in particular changes in growth hormone secretion (GH, IGF-1) in the regulation of body composition, potentially via its negative regulation on muscle. See growth factor (IGF-1) production and activity.

### 2 Preliminary Findings

In preclinical studies we have found that female C57BL/6 mice administered tamoxifen containing BC treatment (200mg/kg) cyclophosphamide, epirubicin, and 500 mg/m<sup>2</sup> 5-fluorouracil (CAF), exhibit a change in body composition and increased fat-free mass, similar to that seen in BC patients.

### 3 Aims

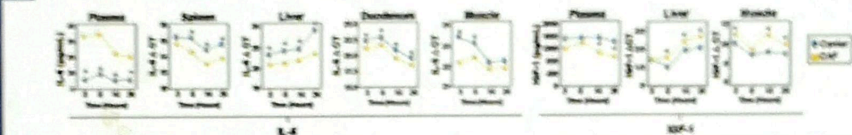
To generate pre-clinical data concerning the role of IGF-1 and IGF-1 in breast cancer treatment-related changes in body composition.

### 5 Figure 2. IGF-1 mediates the effects of CAF on systemic IGF-1 levels.



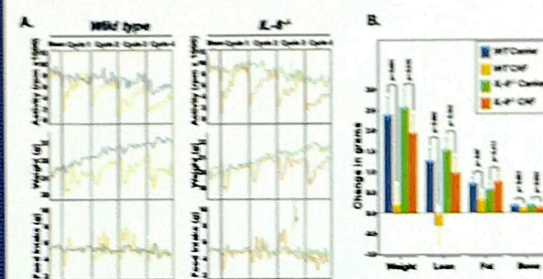
20-week-old female C57BL/6 mice and female mice and male E-4<sup>-/-</sup> C57BL/6 mice (Jackson Laboratories, Bar Harbor, ME) were administered cyclophosphamide (200mg/kg), epirubicin (mg/kg), and 5-fluorouracil (500 mg/m<sup>2</sup>) by intraperitoneal injection, while an additional 10 mice were sham-treated. At 14, 21, 28, and 35 days post-treatment plasma IGF-1 levels were measured by ELISA and relative IGF-1 levels in liver and skeletal muscle were measured by qRT-PCR. Differences between levels of IGF-1 and IGF-1 by group were analyzed using a two-tailed t-test at the 0.05 confidence interval. Data are presented as the mean ± standard error of the mean. p < 0.05 was considered to be statistically significant. Note that plasma levels of IGF-1 do not decrease in E-4<sup>-/-</sup> deficient mice compared to control.

### 4 Figure 1. Breast cancer chemotherapy (CAF) induces systemic increase in IGF-1 production in mice.



Forty-eight male and female C57BL/6 mice (Jackson Laboratories, Bar Harbor, ME) were administered cyclophosphamide (200mg/kg), epirubicin (mg/kg), and 5-fluorouracil (500 mg/m<sup>2</sup>) by intraperitoneal injection, while an additional 10 mice were sham-treated. At 0, 14, 21, 28, and 35 days post-treatment plasma levels of IGF-1 and IGF-1 protein in plasma by immunoblotting and relative levels in skeletal muscle, liver, and skeletal muscle by quantitative real-time reverse transcription-PCR (qRT-PCR). Differences between levels of IGF-1 and IGF-1 by group were analyzed using a two-tailed t-test at the 0.05 confidence interval. Data are presented as the mean ± standard error of the mean. p < 0.05 was considered to be statistically significant. (\*) Note the systemic increase in IGF-1 production in response to CAF treatment, while IGF-1 production is decreased.

### 6 Figure 3. IGF-1 deficient mice treated with CAF appear to be protected from loss of lean body mass.



Twenty female E-4<sup>-/-</sup> mice and 20 WT counterparts were housed singly in home cages fitted with a running wheel, allowing measurement of daily physical activity levels. Baseline food intake, body weight and activity level were measured over a 70-day period prior to drug administration. On day 11, 10 of the E-4<sup>-/-</sup> deficient mice were administered cyclophosphamide (200mg/kg), epirubicin (mg/kg), and 5-fluorouracil (500 mg/m<sup>2</sup>) by intraperitoneal injection, the remaining 10 were sham-treated. WT mice underwent the same procedure. The effects of CAF administration on daily food intake, physical activity, and body weight were determined during the course of 4 treatments administered at 2-week intervals. B) The effects of CAF administration on changes in body composition were measured by measuring total lean body mass, total fat mass, and total bone mineral content by Dual Energy X-ray Absorptiometry (DEXA) using a Lunar PIXImus 3 just prior to the first drug dose and 2-weeks after the last drug dose. The change in lean body mass, fat mass, and bone mass is shown after controlling for total food intake and total physical activity level throughout the treatment phase. Note that in contrast to WT mice, E-4<sup>-/-</sup> deficient mice treated with CAF appear to be protected from loss of lean body mass.

### 7 Conclusion

Our findings demonstrate that a commonly used BC treatment can upregulate the production of IGF-1 in several different organ systems (including skeletal muscle) and decrease systemic levels of IGF-1. The effect of IGF-1 induction using CAF treatment on systemic IGF-1 levels may be the mechanism underlying loss of lean body mass that commonly occurs in women undergoing treatment for BC with systemic antineoplastic drugs. Therefore, this work has the potential to lead to new treatment strategies aimed at decreasing the effects of drug treatment on muscle loss.

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