

# Intermittent Fasting for ovarian cancer reduction

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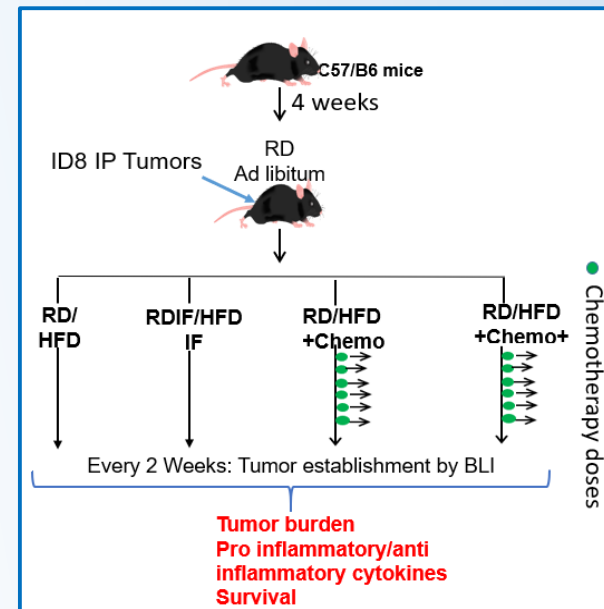
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## Introduction

Despite the advances made in Epithelial Ovarian Cancer (EOC) therapy, the five-year survival rate has been stagnant at approximately 45% for decades. The current standard therapeutic approach of platinum and taxane after surgery, while beneficial, is accompanied by toxic side effects. Also, the high cost of chemotherapy results in financial toxicity resulting in lower quality of life and limiting access to the highest quality care. Dietary Interventions have emerged as significant in modulating outcomes in several cancers, but a strong link connecting diet and EOC is sparse. There are no established recommendations on dietary regimens that would be beneficial and improve the survival rate of EOC patients. Dietary intervention through *caloric restriction* has a strong capacity to alter the responses of cancer cells and the microenvironment. Our lab established that a 30% chronic calorie restriction without malnutrition reduced EOC progression and improved metabolic and cytokine profile in the ID8 syngeneic model. Our **aim** here was to investigate if *dietary restriction by intermittent fasting (IF)* regimen of 16h fast 5-days/ week results in reduced EOC progression and increased overall survival relative to non-fasted mice by decreasing systemic metabolic growth factors, inflammatory cytokine signature and improving anti-tumor immune response. Preclinical studies and clinical trials have shown that intermittent fasting has broad-spectrum benefits for many health conditions, such as obesity, diabetes mellitus, cardiovascular disease, cancers, and neurologic disorders.

## Methods

Female B6 mice were fed on Regular diet (RD) and High fat diet (HFD) and were injected peritoneally with 5 million mouse epithelial ovarian cancer ID8-Luc2 cells were subjected to 16 hour fasting for 5days/week alone or in combination with carboplatin (Fig. 1). Tumor growth was monitored by in situ luciferases guided imaging. Changes in growth factors and cytokines was determined by ELISA and immune response measured by flow cytometry.

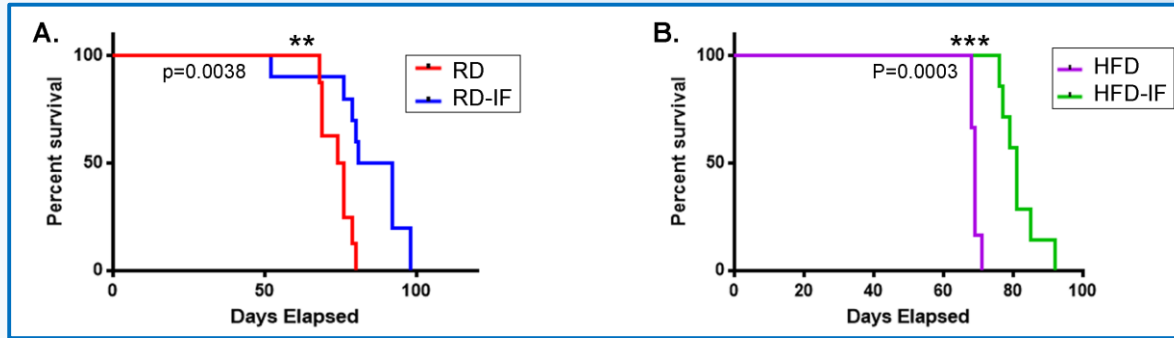


## Schematic of mouse groups and plan.

- Mice were subjected to regular diet (RD) or High fat diet (HFD), Intermittent fasting (IF) combined with RD and HFD, Chemotherapy (carboplatin 10mg/kg body weight) combined with RD and HFD, IF combined with chemotherapy treatment and RD/HFD.
- In situ luciferase guided imaging was done to measure bioluminescence (BLI) as indicator of tumor burden.
- Tissue, ascetic fluid and blood was collected for further analysis.

# 1. Intermittent Fasting Reduces Tumor Burden and Improves Survival in a mouse model of Ovarian Cancer, Irrespective of the Diet.

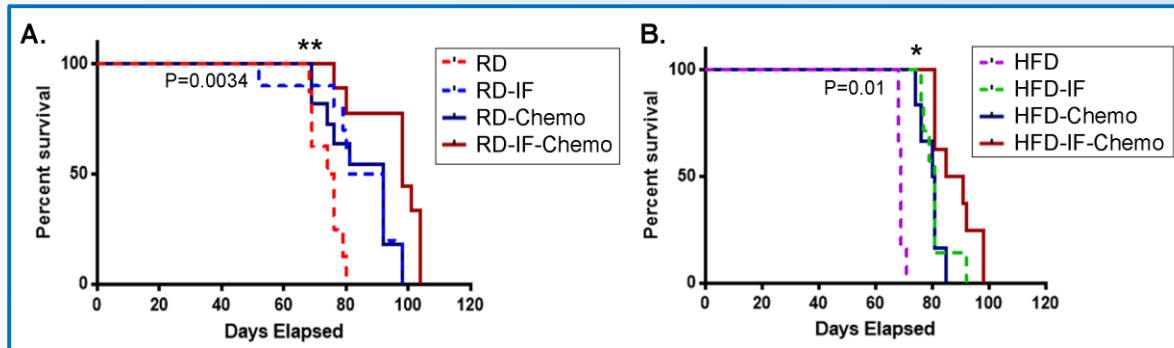
1.1



## 1.1 Intermittent fasting improved overall survival

- (A) Tumor bearing mice subjected intermittent fasting (IF) and fed a balanced regular diet (RD) showed significant increase in overall survival (OS) with an increase in median survival of 86.5 days (IF) compared to 75 days (RD).
- (B) Tumor bearing mice subjected intermittent fasting (IF) and fed a high fat diet (HFD) showed significant increase in OS with an increase in median survival of 81 days (IF) compared to 69 days (RD).

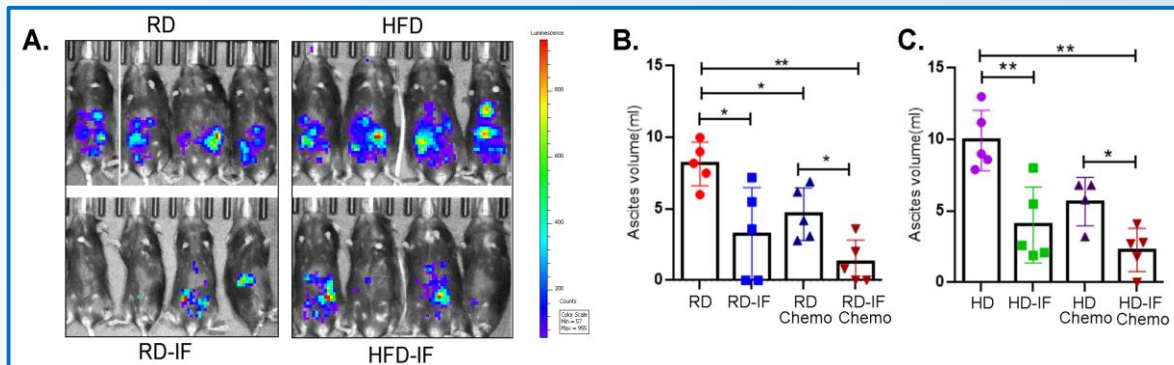
1.2



## 1.2 Intermittent fasting enhances chemotherapy

- (A) Tumor bearing mice subjected intermittent fasting (IF) and fed a balanced regular diet (RD) in combination with chemotherapy further improved the OS with an increase in median survival of 99.5 days (chemotherapy+ IF) compared to 92 days (Chemo alone).
- (B) Tumor bearing mice subjected intermittent fasting (IF) and fed a high fat diet (HFD) in combination with chemotherapy further improved the OS with an increase in median survival of 87 days (chemotherapy+ IF) compared to 75 days (Chemo alone).

1.3

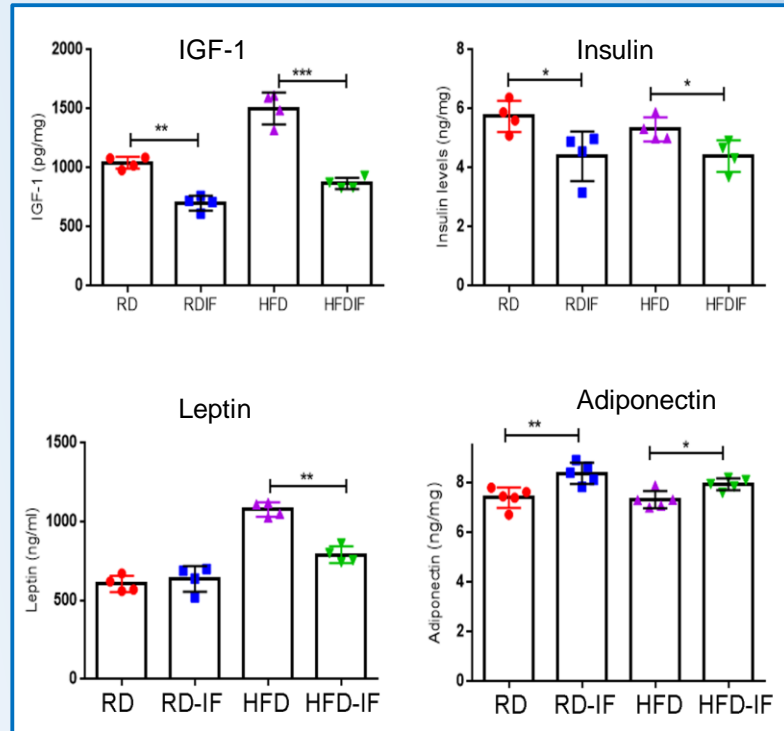


## 1.3 Intermittent fasting reduces tumor burden

- (A) Bioluminescence images (BLI) show reduced tumor burden in mice subjected to intermittent fasting (IF) and fed a balanced regular diet (RD, left panel) or a high fat diet (HFD) compared to mice that did not undergo IF.
- (B) (C) Mice subjected IF and fed a balanced regular diet (RD, B), or a high fat diet (HFD, C) compared to mice that did not undergo IF had reduced ascetic fluid accumulation..

## 2. Intermittent Fasting Reduces Metabolic Growth Factors and Inflammatory Cytokines, Irrespective of the Diet.

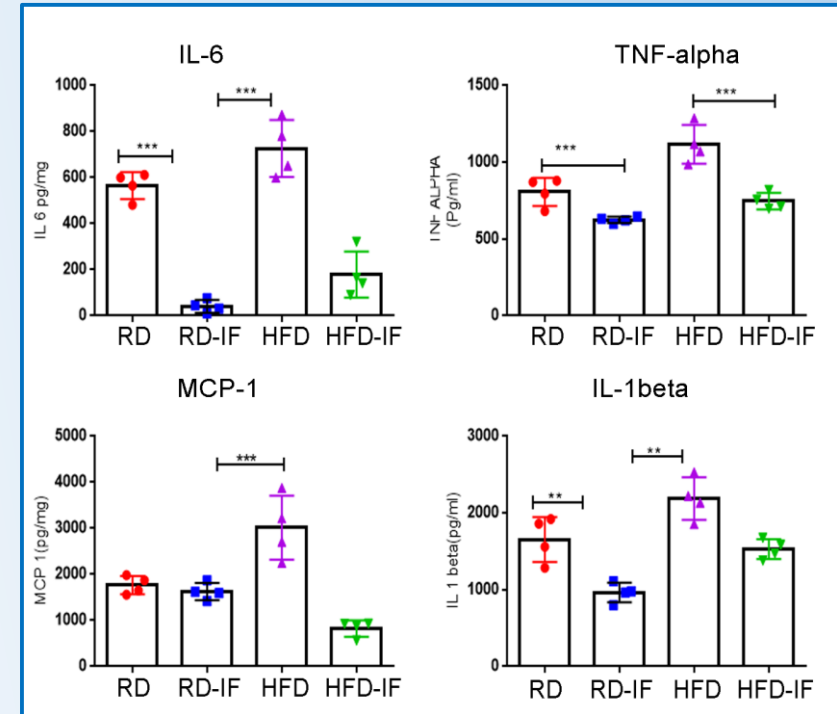
### 2.1



### 2.1 Intermittent fasting reduce metabolic growth factors

Tumor bearing mice subjected intermittent fasting (IF) and fed a balanced regular diet (RD) or a high fat diet (HFD) had reduced metabolic growth factors like IGF-1 (Insulin growth factor 1), insulin, leptin and adiponectin in the tumor microenvironment. The growth factors were measured by ELISA in the ascites collected from mice. All these growth factors are known to be increased in ovarian cancers. IGF-1 and insulin are the canonical factors affected by caloric reduction.

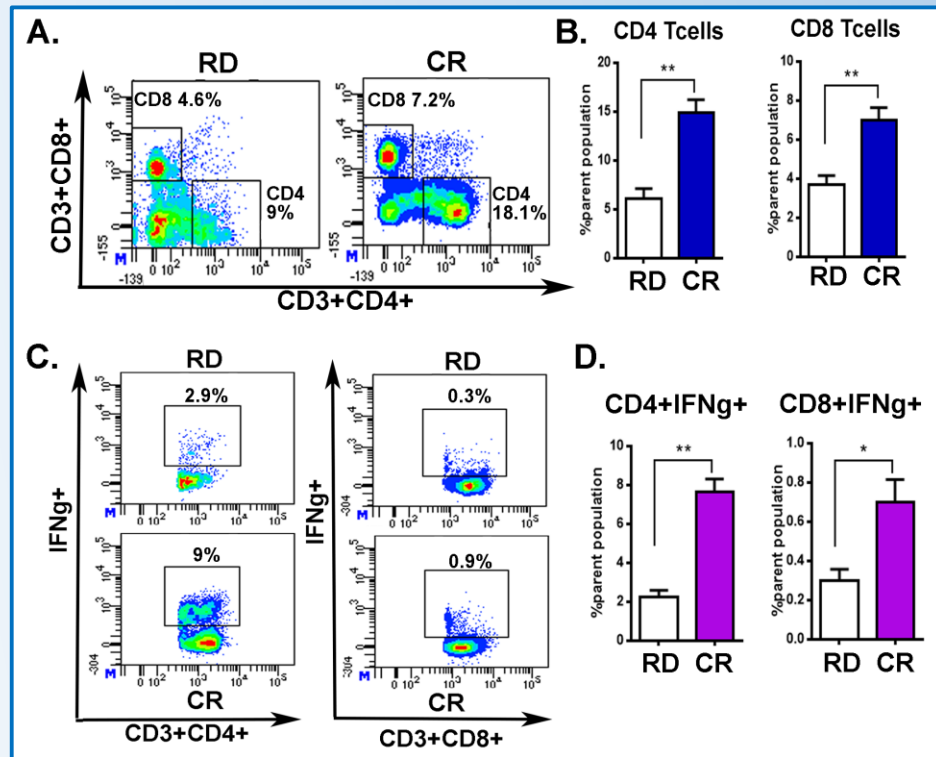
### 2.2



### 2.2 Intermittent fasting reduce metabolic growth factors

Tumor bearing mice subjected intermittent fasting (IF) and fed a balanced regular diet (RD) or a high fat diet (HFD) had reduced inflammatory cytokines like IL-6 (Interleukin 6), TNFalpha (Tumor necrosis factor), MCP-1 (Macrophage chemoattractant factor 1) and IL1beta (Interleukin 1beta) in the tumor microenvironment. The cytokines were measured by ELISA in the ascites collected from mice. All the inflammatory cytokines are known to be increased in ovarian cancers. IL6 and TNFalpha are the canonical factors affected by caloric reduction.

### 3. Caloric Restriction Improves Anti-Tumor Immune Response



#### Caloric restriction increases T cells in the tumor

Flow Cytometry analysis of ascites from the RD and fasting groups showed an increase in the frequency of CD4 T-helper cells and CD8 T cytotoxic cells (A) is a representation of the separated populations by flow cytometry. (B) is the bar graph representation of T cells % in 3 samples. (C) is a representation of the IFNγ expressing T-cells separated populations by flow cytometry (B) is the bar graph representation of IFNγ expressing T cells % in 3 samples. Expression of IFNγ is an indicator of T cell activation.

### 4. Summary and Conclusions

- Calorie Restriction by Intermittent Fasting restricts cancer growth & significantly improves survival of ovarian tumor bearing mice.
- This effect appears to be associated with reduction in tumor promoting factors (growth factors, hormones and cytokines).
- And suggestive to be associated with rearrangement of immune environment, specifically increase in T-cells frequency and activation.

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