

## Introduction

According to the American Cancer Society, in 2022 about 21,000 women will receive an ovarian cancer diagnosis this year and about 13,000 women will die from ovarian cancer. And unfortunately, up to 85% of the women who undergo aggressive treatment – surgery, chemotherapy, and/or radiation – for advanced ovarian cancer face the risk of recurrence after initial treatment. However, Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) are currently approved for the treatment of advanced breast cancers, ovarian cancers, and pancreatic tumors harboring BRCA1 or BRCA2 (BRCA1/2) mutations [1-6]. So, right now these drugs only help about 50% of patients with ovarian cancer; specifically, those who have completed initial treatment with surgery and chemotherapy and have homologous recombination deficiency (HRD) or BRCA mutations.

So, it is important to find more biomarkers and targetable PARPs for patients with other forms of ovarian cancer to benefit from the cancer preventive effects of PARPis. Interestingly, recent published studies from Dr. Guang Peng's laboratory and other groups have revealed a previously unknown function of PARPis as immunomodulating agents through activation of the DNA sensing cyclic GMP-AMP Synthase (cGAS)-stimulator of interferon genes (STING) pathway [7-10]. The activation of this immune response in turn enhances T cell proliferation and trafficking to the tumor microenvironment [11,12]. Thus, PARPis can indirectly stimulate antitumor immunity by enhancing the recruitment of cytotoxic T-cells in both BRCA wildtype and mutant cancer cells [10].

Based on preliminary studies, we hypothesize that PARPis will induce a transcriptional program of immune responses through the cGAS-STING-TBK1-IRF3 pathway and active anti-tumor immunity in BRCA wildtype ovarian tumors as a preventive agent for recurrence.

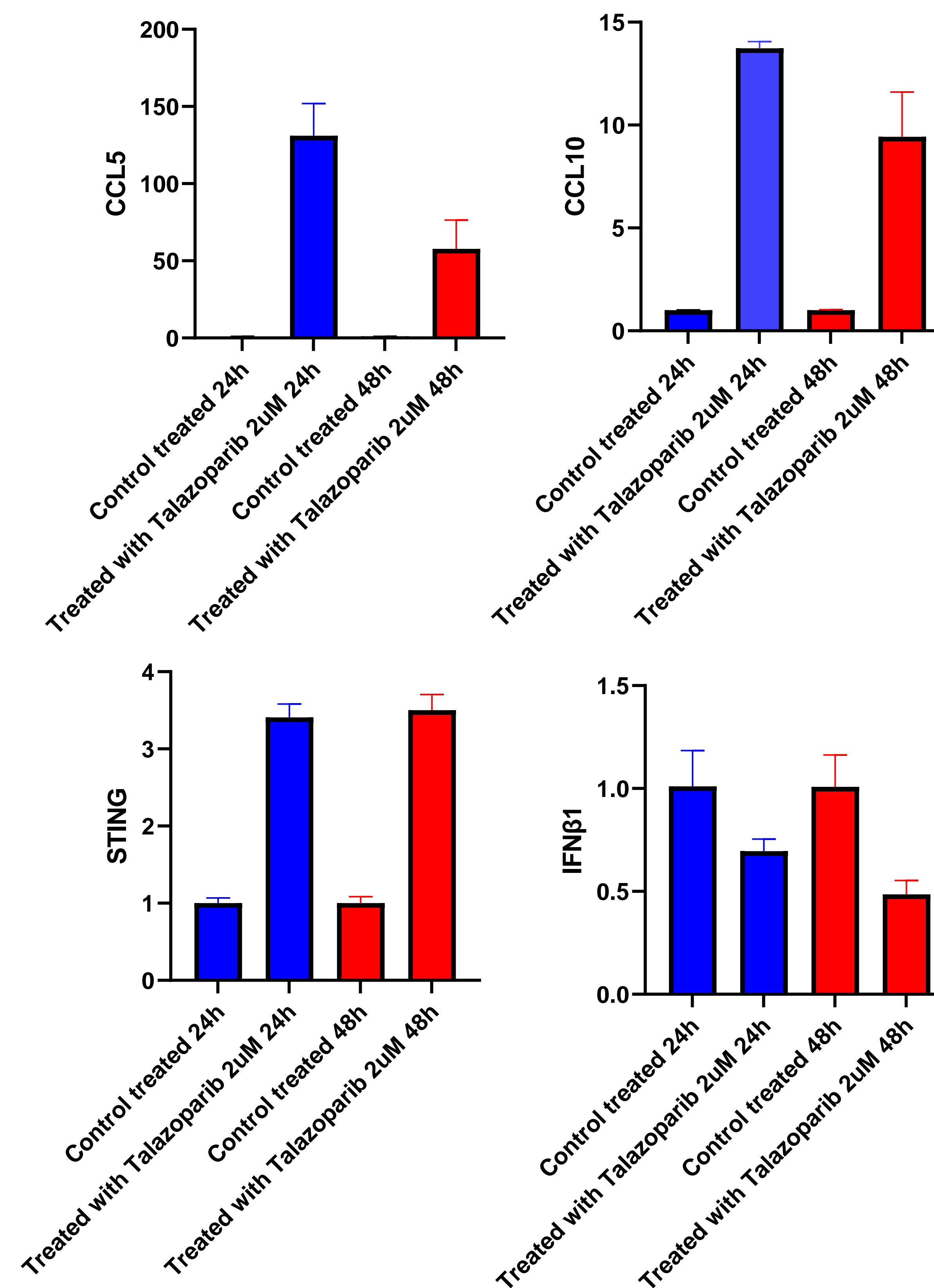
## Methods

(1) Ovarian Cancer cell cultures will be used as a model to test molecular effects. BRCA1 knockdown cells will be used as a control and compared to BRCA wild type cells. These cells will be treated with different dosages of PARPis.

(2) We will use cell models to test whether PARPis may lead to an enhanced innate immune signaling in ovarian cancer cells by using RT-PCR to detect CCL5 and CXCL10.

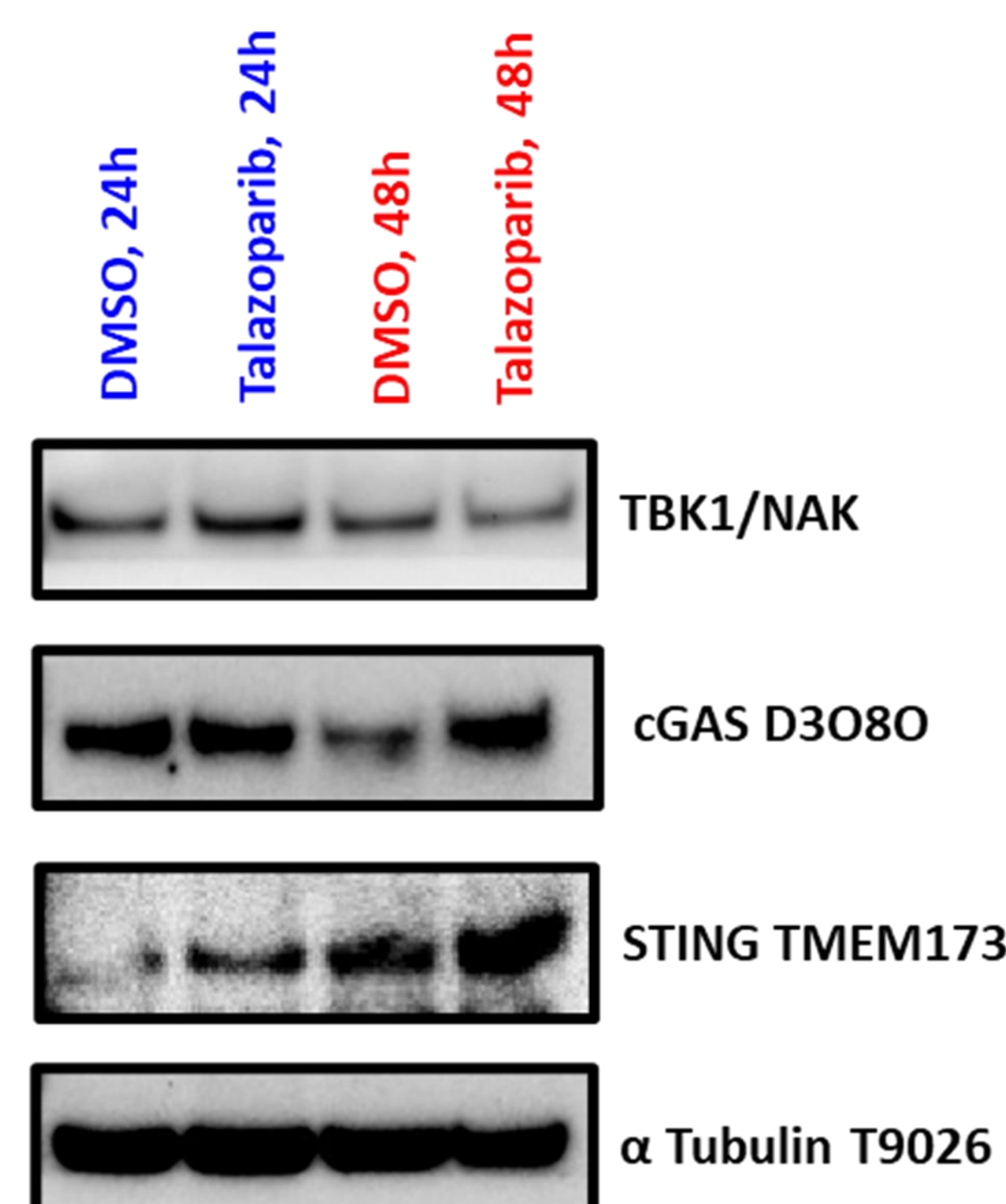
(3) We will use cell models to test whether PARPis may lead to an enhanced innate immune signaling in ovarian cancer cells by using Western blot to detect p-TBK1/TBK1 and p-IRF3/IRF3.

## Results



**Fig. 1 Treatment with Talazoparib associated with**

- ↑CCL5 (145X at 24h, 70X at 48h)
- ↑CXCL10 (13X at 24h, 10X at 48h)
- ↑STING (3.5X at 24h and 48h)
- ↓IFNβ (0.75X at 24h, 0.5X at 48h)



**Fig. 2 Treatment with Talazoparib associated with**

- ↑TBK1 (more prominent at 24h)
- ↑cGAS (more prominent at 48h)
- ↑STING (more prominent at 48h)

## Conclusions

Results from this project will provide novel mechanistic insights into the therapeutic efficacy of PARPis as immunomodulating agents. This concept of the underlying mechanism of PARPis will provide strong rationale to develop predictive biomarkers and preventive effects of PARPis for patients with other forms of ovarian cancer beyond BRCA deficiencies.

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