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CX-5461 can destabilize replication forks in PARP inhibitor-resistant models of ovarian cancer

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\textbf{ABSTRACT}

Acquired drug resistance leads to poor clinical outcome in high grade serous ovarian cancer (HGSOC). We have demonstrated the efficacy of the novel drug CX-5461 in HGSOC is mediated through destabilization of DNA replication forks. The data highlights the potential of CX-5461 in overcoming a general mechanism of chemotherapeutic resistance.

\textbf{Authors’ view}

High grade serous ovarian cancer (HGSOC) is the most aggressive subtype of ovarian cancer (OvCa) accounting for 70–80% of all cases. Only 46% of women with HGSOC survive for more than five years. The high mortality rate of OvCa is due to late diagnosis and the lack of effective treatment options for resistant disease.

\textbf{Treatment responses are variable in HGSOC}

The standard therapy of HGSOC involves debulking surgery followed by chemotherapy (combined platinum-based therapy/paclitaxel). Clinical responses are variable, with some patients demonstrating intrinsic resistance to chemotherapy, while others are initially sensitive but later develop aggressive, therapy-resistant disease within 2 years. Chemotherapy is most effective in cancers with defects in DNA damage repair including alterations in homologous recombination (HR) DNA repair genes, most frequently \textit{BRCA1/2} (Breast Cancer gene1/2). Poly-ADP ribose polymerase (PARP) inhibitors (PARPi) have improved progression free survival in \textit{BRCA}-mutated OvCa. PARPis are currently used as maintenance therapy following complete or partial response to chemotherapy in recurrent HGSOC. However, acquired resistance to PARPi is common, involving multiple mechanisms, including increased drug efflux, decreased PARP trapping, reestablishing replication fork stability (fork protection) and re-activation of HR. Fork protection confers general resistance to chemotherapeutics and therefore represents a fundamental barrier to the cure of HGSOC.

\textbf{Ovarian cancer requires a bold new strategy}

Our recently published data demonstrate the novel small molecule drug CX-5461 has promising potential as a new class of targeted therapy for HGSOC. \textsuperscript{3} CX-5461 specifically targets RNA polymerase I transcription (Pol I) of ribosomal RNA (rRNA) genes, which produces the 18S, 5.8S and 28S rRNA components of the ribosome. The first-in-human Phase I dose escalation study of CX-5461 in patients with advanced hematological malignancies showed CX-5461 led to disease stabilization in a third of trial participants, reinforcing its potential as an anti-cancer therapy. \textsuperscript{4} CX-5461 is also in Phase I clinical trial in solid tumors and has shown preliminary activity in patients with HR-deficient tumors. \textsuperscript{5} Indeed, we demonstrated CX-5461 is synthetic lethal with HR deficiency in \textit{in vitro} and \textit{in vivo} models of HGSOC. \textsuperscript{3} We have demonstrated CX-5461 has a different sensitivity profile to PARPi involving activation of localized DNA damage response (DDR) at the rRNA genes (rDNA) within the nucleoli, the site of Pol I transcription. \textsuperscript{3,6} CX-5461 prevents Pol I from binding to the highly repetitive rDNA repeats creating chromatin defects leading to activation of ATR (Ataxia telangiectasia and Rad3) and ATM (Ataxia telangiectasia-mutated) at the nucleoli\textsuperscript{5,6} (Figure 1). The net results of CX-5461-mediated DDR is replication stress associated with destabilization of DNA replication forks leading to DNA damage and cell cycle arrest in HR-proficient HGSOC cells and cell death in HR-deficient cells due to exacerbated DNA damage levels. Recently, the sensitivity profile of CX-5461 was shown to closely resemble a topoisomerase II (TOP2) poison. \textsuperscript{7} It is possible that CX-5461 selectively traps TOP2 at the highly transcribed rRNA genes and to some extent across the genome. Future studies on understanding the role of TOP2 in CX-5461-mediated replication stress are important for optimal design of combination therapies that will be more effective in HR-proficient HGSOC.
CX-5461-induced replication stress targets fork stability in HGSOC

In our recent study, we have shown CX-5461 enhances the therapeutic efficacy of PARPi in HR-deficient HGSOC preclinical models in vitro and in vivo. We propose CX-5461 and PARPi combination will provide a more effective therapy in HR-deficient HGSOC than single-agent treatment. Further, CX-5461 exhibited significant single-agent therapeutic efficacy in a HGSOC-patient derived xenograft (PDX) with reduced sensitivity to cisplatin and the PARPi olaparib by overcoming replication fork protection.

Recent studies in patient-derived HGSOC organoids identified fork stability, measured following treatment with replication stalling agents, as a biomarker of response to chemotherapy and inhibitors of ATR and CHK1 (checkpoint kinase 1). In Hill et al, seventeen of twenty eight (61%) of HGSOC organoids had unstable forks and this phenotype was associated with sensitivity to carboplatin and inhibitors of ATR and CHK1. In contrast, organoids with stable forks were resistant to carboplatin, ATR and CHK1 inhibitors. Therefore, our findings demonstrating CX-5461’s efficacy in HGSOC cells derived from cisplatin- and olaparib-resistant PDX with stable forks suggest CX-5461 is a promising therapy in resistant HGSOC with a distinct sensitivity profile in targeting replication fork stability compared to chemotherapy and PARPi. Moreover, CX-5461 could potentially have improved efficacy in combination therapy with ATR and CHK1 inhibitors in relapsed HGSOC via enhanced targeting of fork stability.

While, CX-5461 represents an exciting therapeutic option for HGSOC, we believe the identification of predictive biomarkers of response to identify patients who will benefit from this therapy is essential for the success of future clinical trials. We have identified CX-5461-sensitivity signatures that comprise BRCA1-mutated and MYC targets gene expression signatures to be enriched in a subset of primary and relapsed OvCa. We have also shown that high rates of Pol I transcription and active rDNA chromatin status determine sensitivity to CX-5461 in OvCa cell lines. MYC is a master regulator of Pol I transcription and we have shown that upregulation of Pol I transcription is required to drive malignant transformation in MYC-driven lymphoma. Our data therefore suggest MYC-driven Pol I transcription and/or MYC-driven global transcription and replication stress underlie sensitivity to CX-5461. We propose that CX-5461 has exciting potential as a treatment option for a subset of patients with OvCa harboring high levels of replication stress and/or high MYC activity, which is typically associated with poor clinical outcome.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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