FACT Inhibition with CBL0137 as a Novel Therapeutic Strategy for Aggressive-Variant Prostate Cancer

Brett Hollier[1], Md Mominur Rahman[1], Sayuri Herath[1], Yu Hin Tang[1], Anja Rockstroh[1], Charles Bidgood[1], Marianna Volpert[1,2], Ellca Rather[1], Michelle Maugham-Macan[3], Nataly Stylianou[1], Ladan Fazli[4], Arun Azad[5], Himisha Beltran[6], Martin Gleave[4,7], Yuzhuo Wang[4,7], Eva Corey[8], Katerina Gurova[9], Melanie Lehman[1], Jennifer Gunter[1] and Colleen Nelson[1]

Affiliations

1. Australian Prostate Cancer Research Centre-Queensland, Translational Research Institute, Centre for Genomics and Personalised Health, School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia.
2. The John Curtin School of Medical Research, The Australian National University, Canberra, ACT, Australia.
3. School of Health and Behavioural Sciences, University of the Sunshine Coast, Sunshine Coast, QLD, Australia.
4. Vancouver Prostate Centre, Vancouver, BC, Canada.
5. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia.
6. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
7. Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada.
8. Department of Urology, University of Washington, Seattle, Washington, USA.
9. Department of Cell Stress Biology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA.

Background

A significant proportion of metastatic castration-resistant prostate cancer (mCRPC) evolves into aggressive-variant prostate cancer (AVPC), including treatment-emergent neuroendocrine prostate cancer (tNEPC) and double-negative prostate cancer (DNPC). These anaplastic subtypes are highly lethal, display resistance to current androgen receptor–directed therapies, and lack durably effective targeted treatments. The FAcilitates Chromatin Transcription (FACT) complex is upregulated in AVPC, representing a potential novel therapeutic target. CBL0137, a small-molecule curaxin that inhibits FACT, has shown favorable tolerability in early clinical testing and may provide a new therapeutic avenue for these aggressive disease states.

Methods

We evaluated the antitumor efficacy of CBL0137 in a panel of patient-derived xenograft (PDX) and PDX-derived organoid (PDXO) models that recapitulate AVPC phenotypes, including tNEPC and DNPC. CBL0137 was administered intravenously to PDX-bearing mice, and tumor growth and survival endpoints were monitored. Parallel PDXO dose-response assays were performed to establish the IC50 values. Cisplatin sensitivity was assessed in organoid cultures to guide planned combination therapy studies. Multi-omic pipelines (RNA-seq, ATAC-seq, methylation, and SNP arrays) were refined to define CBL0137-driven molecular alterations.

Results

CBL0137 significantly suppressed tumor growth across four independent AVPC PDX models (LTL-545, LTL-370, LTL-331R, and LuCaP.49), resulting in decreased tumor volumes and weights, prolonged doubling times, and reduced tumor burden over the treatment course. PDXO assays confirmed the potent activity of CBL0137, with IC50 values in the low micromolar range (0.52–1.71 μM), alongside evidence of increased tumor cell death. Cisplatin organoid assays demonstrated model-dependent responses, with IC50 values between 1.68–7.67 μM. Currently, in vivo cisplatin optimization and CBL0137–cisplatin combination therapy preclinical studies are being conducted. Early integrative analyses of multi-omic datasets highlighted transcriptomic and epigenomic perturbations consistent with the disruption of chromatin regulation by CBL0137, leading to effects on cellular differentiation and neuronal lineage pathways.

Conclusions

FACT inhibition with CBL0137 demonstrated strong preclinical efficacy in AVPC models, including tNEPC and DNPC. These findings support the potential of CBL0137 as a promising therapeutic candidate for aggressive, treatment-emergent prostate cancer. Ongoing studies will determine whether CBL0137 enhances cisplatin response and provide mechanistic insights into its activity through multi-omic profiling, with the ultimate aim of informing early phase clinical development.

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Conflicts of Interest Disclosure Statement

None to declare