The Canady Helios Cold Atmospheric Plasma in Combination with Senescence Inducing Drug CPI203 Regimen for the Treatment of Drug Resistance Cancers

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Introduction

Combinations of drugs are used for cancer resistance. Different susceptibilities are targeted with various combinations to improve efficacy; however, toxicity has been a major issue with such approach. Sequential treatment regimen consisting of a senescence inducing drug in combination with a second therapy such an immunotherapy that selectively kills senescent cancer cells could be used to counter toxicity during cancer therapy. Induction of cell death and immune stimulation in cancer cells without perturbance of normal cells by Cold Atmospheric Plasma has been well documented. In this study we used Canady Helios Cold Plasma (CHCP) in combination with senescence inducing drug CPI203 for treating cancer cells that are fairly resistant to CHCP treatment alone.

Method

Various combinations of CPI203 concentration and CHCP power and time of incubations were tested.
Cell viability test (MTT assay)
Apoptosis occurrence (Caspase Assay).
Real time cell cycle analysis (Incucyte)
Gene expression profile (qRT-PCR)

Cell Lines

Cell Line	Description
MDA-MB-231	Human Breast Adenocarcinoma cells
Hs574T	Human Breast Ductal Carcinoma cells
BT-474	Human Breast Ductal Carcinoma cells
HepG2	Human Hepatocellular Carcinoma cells
BxPC-3	Human Pancreatic Adenocarcinoma cells

Cell Viability

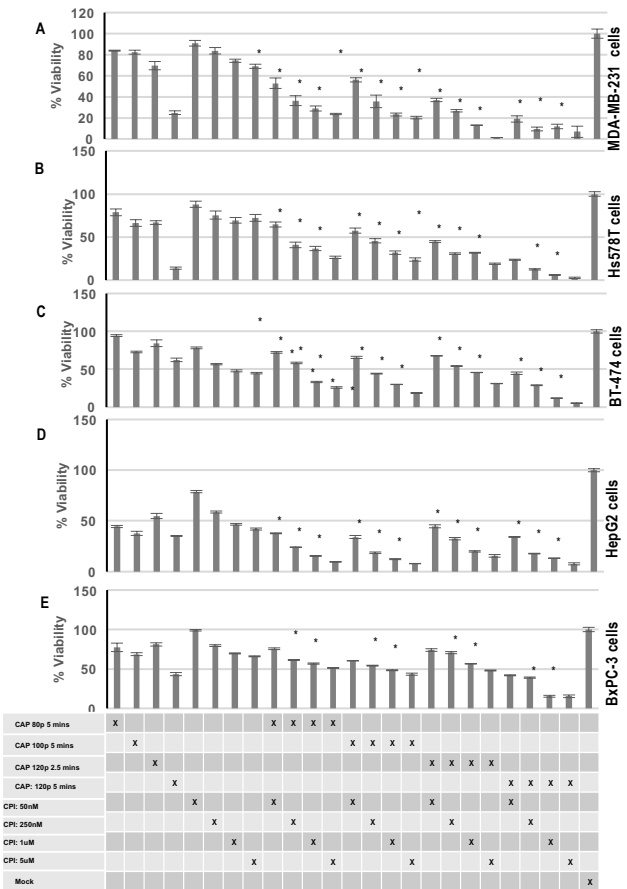

Fig. 1 Viability of CPI203-CHCP-treated cells at various concentrations, power and time of treatment. (A) MDA-MB-231, (B) Hs578T, (C) BT-474, and (D) HepG2 and (E) BxPC3 cells after 48 hr, compared to CHCP treated cells. Cells were seeded at a concentration of 1 x 10^5 cells/well into 12-well plates and viability was measured by MTT assay. CPI203 increased the the potency of CHCP at all the power settings (* $p < 0.05$).

Apoptosis

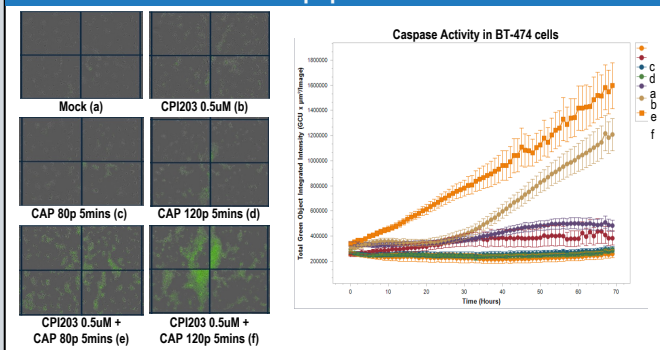

Fig. 2 Representative images and graph of Caspase activity of BT-474 cells at 0.5uM CPI203 concentrations and 80p and 120p CHCP power for 5 mins of treatment. Graph showing Kinetics of caspase-3 activity. Combination of CPI203-CHCP treatment at 80p and 120p 5mins show a significant increase in caspase activity compared to either treatment alone ($p<0.05$).

Senescence

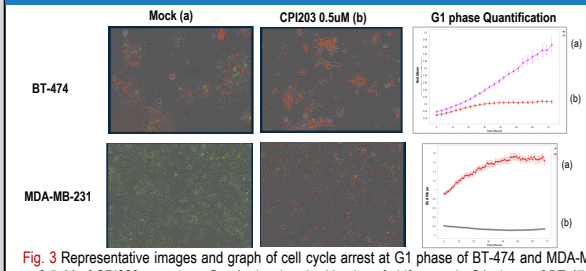

Fig. 3 Representative images and graph of cell cycle arrest at G1 phase of BT-474 and MDA-MB-231 cells at 0.5uM of CPI203 treatment. Graph showing the kinetics of shift towards G1 phase of BT-474 and MDA-MB-231 cells after CPI203 treatment

Cell Cycle

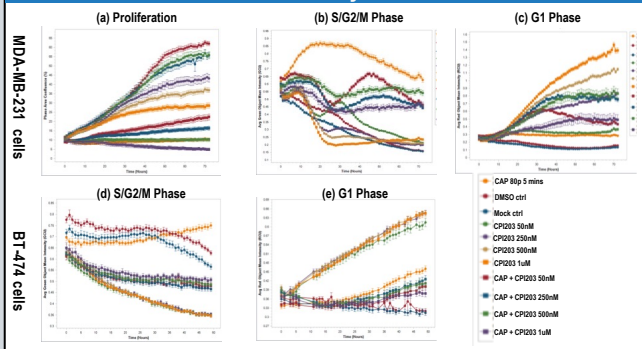

Fig. 4 Graph showing quantification of cell proliferation and G1 phase (Red), S/G2/M (Green) phase of cell cycle of BT-474 and MDA-MB-231 cells at various CPI203 concentrations and 80p CHCP power for 5 mins of treatment. Graph showing the kinetics cell proliferation, change in cell cycle phases with or without the combination of CPI203-CHCP treatment.

Gene Expression

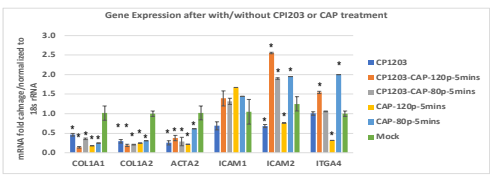

Fig. 5 Graph showing quantification of cell adhesion markers mRNA expression in BT-474 cells at 0.5uM CPI203 concentrations and 80p and 120p CHCP power for 5 mins of treatment (* $p < 0.05$).

Conclusion

Our results show that combination of pro-senescence and senolytic treatment by CPI203-CHCP increases the potency of CHCP treatment in CHCP resistant cells. This therapy would be an ideal approach to treat drug resistant cancers with minimal toxicity and warrants further investigation with other pro-senescence drugs-CHCP therapies.

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