NOVEL PAPAVERINE-BASED MITOCHONDRIAL COMPLEX I INHIBITOR SMV-32 ALLEVIATES TUMOR HYPOXIA AND RADIOSENSITIZES HYPOXIC TUMORS

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INTRODUCTION

Radiation therapy (RT) is a standard type of treatment modality used in more than 50% of all cancer patients. However, **tumor hypoxia reduces the effectiveness of RT by limiting the biologically effective dose.**

We identified that established PDE10A inhibitor papaverine (PPV) has an off-target effect inhibiting mitochondrial oxygen consumption (OCR) leading to acute reduction of tumor hypoxia and significant radiosensitization of model tumors.

Because our data show that PDE10A inhibition does not contribute to the effect, we used biomedicinal chemistry approach to engineer its novel derivative SMV-32 with reduced PDE10A inhibitory effect.

MATERIALS AND METHODS

We used Seahorse metabolic flux analyzer to determine the effect of PPV and SMV-32 on mitochondrial OCR in vitro and pODD-luciferase in vivo hypoxia reporter system for pharmacodynamic analyses.

Local radiation therapy was delivered using Small Animal Radiation Research Platform (SARRP).

RESULTS

SMV-32 showed superior OCR inhibition in vitro and enhanced hypoxia reduction in vivo compared to PPV. We observed that a single clinically relevant dose of PPV or SMV-32 significantly reduced the hypoxic fractions of heterotopic and orthotopic tumors in mice and sensitized the tumors to radiation therapy.

CONCLUSION

Both PPV and SMV-32 appear to be promising candidates for clinical radiosensitization. PPV is currently already in phase I clinical trial for treatment of non-small cell lung cancer combined with stereotactic body radiation therapy.

SMV-32 significantly reduced the hypoxic fractions of tumors in mice and sensitized the tumors to radiation therapy.

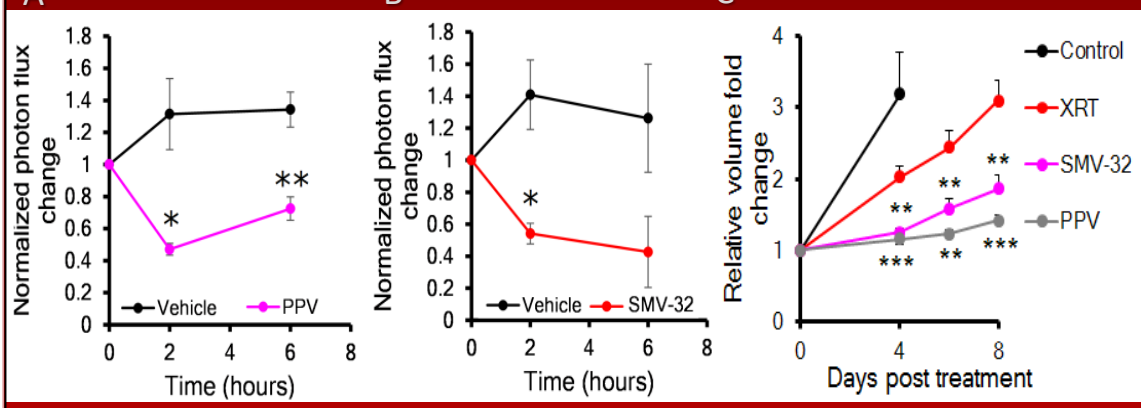

Fig.4 (A-B) Pharmacodynamics analysis of PPV and SMV-32 by In vivo imaging of MiaPaca-2 pODD-Luc expressing orthotopic tumors treated with 2 mg/kg of PPV (A), SMV-32 (B) or vehicle by tail vein injection (n=4); (C) Tumor growth delay of heterotopic EO771 flank tumors in nude mice receiving either 5 Gy XRT (*red*) or 2 mg/kg SMV-32 (*magenta*) or PPV (*gray*) 35 min before 5 Gy XRT (*n* = 8)

Our data support the model that **inhibition of mitochondrial oxidative metabolism leads to reduction of tumor hypoxia with a direct translational potential for mitigating treatment resistance.**

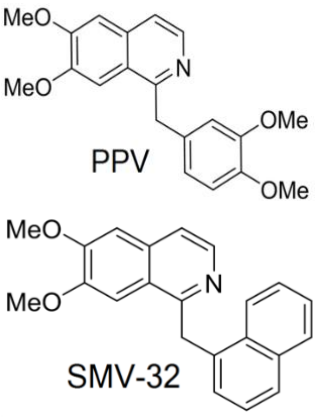

Fig. 1 2D structures of PPV and its novel derivative SMV-32

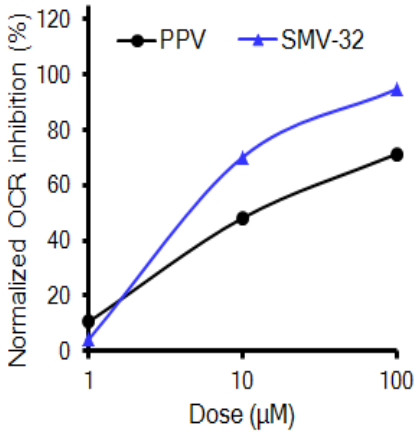

Fig. 2 Mitochondrial OCR inhibition by increasing doses of PPV and SMV-32 in A549 cells by Seahorse, *n* = 5 replicates per group

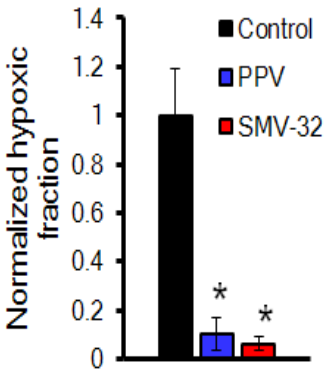

Fig.3 Detection of hypoxic fractions of A549 flank tumors in nude mice treated with 2 mg/kg PPV or SMV-32 (n=5)

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doi:
10.3390/cancers13071696

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