# Therapeutic applications of *SAMMSON* lncRNA inhibition in uveal melanoma

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Shanna Dewaele[1,2], Katrien Vanderheyden[1,2], Boel De Paepe[3], Fariba Nemati[4], Sergio Roman Roman[4], Rudy Van Coster[3], Jo Vandesompele[1,2] and Pieter Mestdagh[1,2]

[1] Center for Medical Genetics, Ghent University, Ghent, Belgium
[2] Cancer Research Institute Ghent (CRIG), Ghent University, Ghent, Belgium
[3] Department of Pediatrics, Division of Pediatric Neurology and Metabolism, Ghent University Hospital, Ghent, Belgium
[4] Translational Research Department, Institut Curie, PSL Research University, Paris, France

## INTRODUCTION

- Most common eye tumor in adults
- Primary treatment: Sx or Rx
- Metastatic disease → survival time < 12 months
- No treatment for metastatic disease
- Melanoma specific lncRNA *SAMMSON*

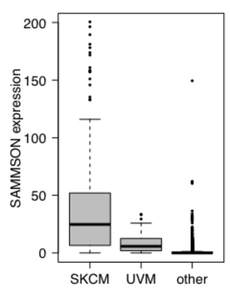


Fig. 1 Sustained upregulation of *SAMMSON* lncRNA expression in skin melanoma (SKCM) and uveal melanoma (UVM) compared to other cancer types

## OBJECTIVE

- Validation of the therapeutic effects of *SAMMSON* inhibition in uveal melanoma
- Evaluation of the effects of *SAMMSON* inhibition on mitochondrial respiration
- Validation of combination therapy including *SAMMSON* inhibition and MEK inhibition

## RESULTS

I *SAMMSON* knock down using LNA antisense oligonucleotides reduces cell viability and induces cell apoptosis

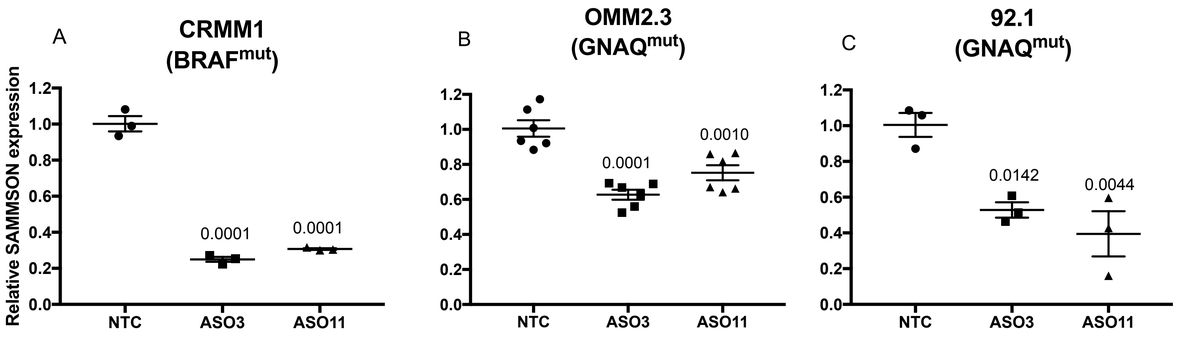


Fig. 2 LNA-based ASO3 and ASO11 treatment result in a knock down of *SAMMSON* expression in conjunctival melanoma cell line CRMM1 (A) and uveal melanoma cell lines OMM2.3 and 92.1 (B, C).

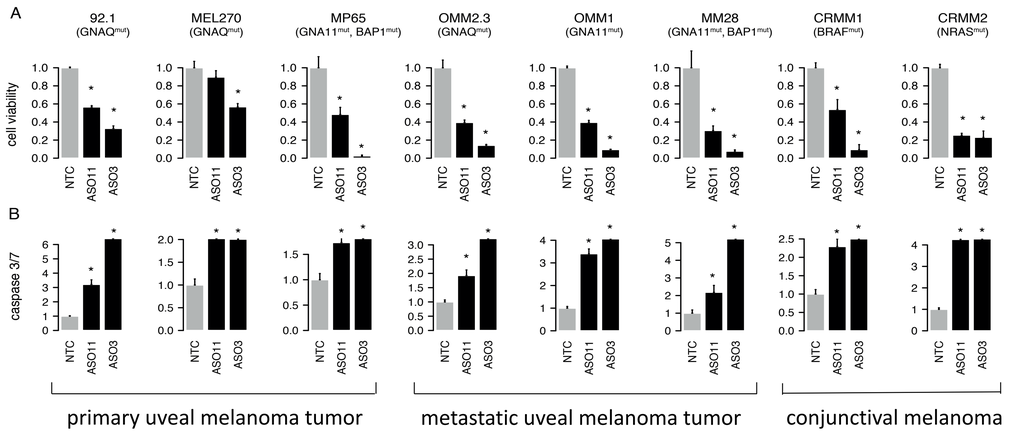


Fig. 3 LNA-based ASO3 and ASO11 reduce the cell viability (A) and induce apoptosis (B) in multiple uveal melanoma and conjunctival melanoma cell lines, independent of the mutational status of the cell line.

II *SAMMSON* knock down results in a decreased mitochondrial respiration

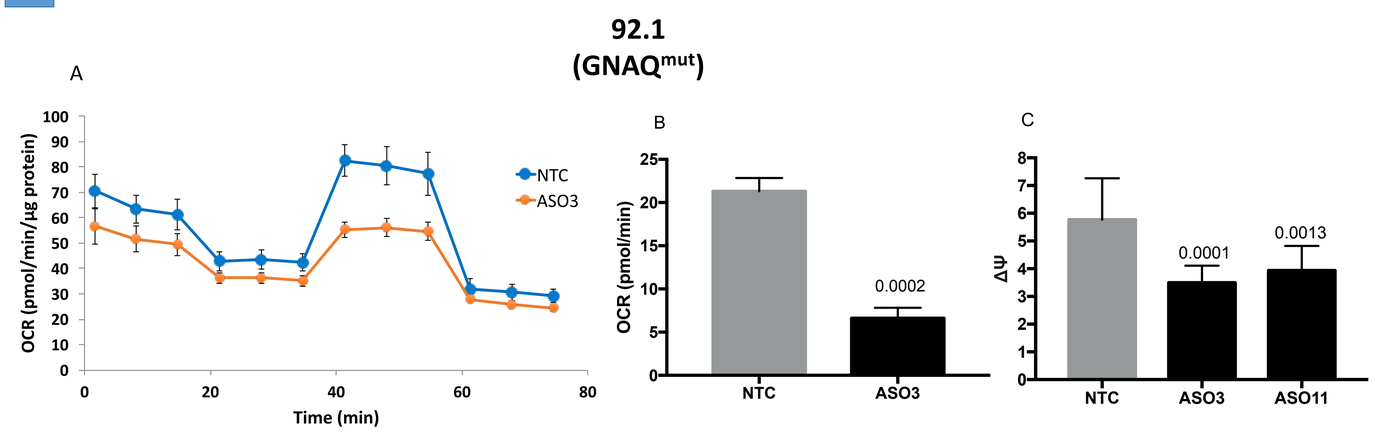


Fig. 4 Two independent methods to investigate mitochondrial function show a decreased mitochondrial respiration upon *SAMMSON* knock down. ASO3 treatment results in an overall decreased oxygen consumption rate (OCR) (A) and significant decreased spare mitochondrial capacity (A,B). Fluorescence imaging of mitochondria demonstrates a decreased electric membrane potential (ΔΨ) upon ASO3 and ASO11 treatment (C).

III Combining *SAMMSON* inhibition and MAPK inhibition results in a synergistic decrease in cell viability

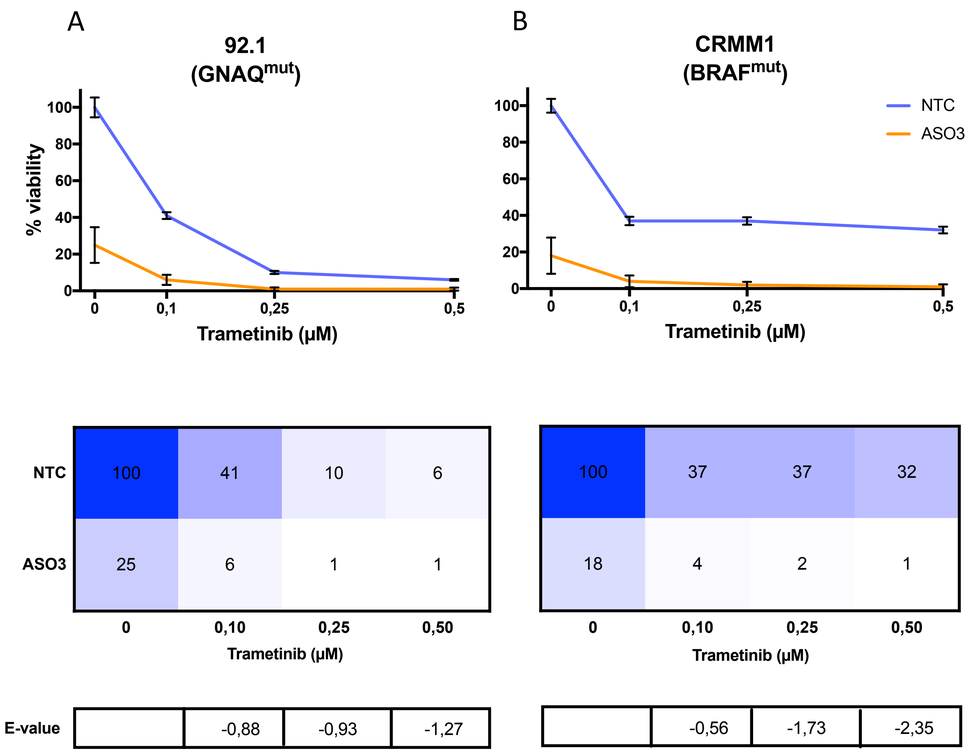


Fig. 5 *SAMMSON* inhibition (ASO3) in combination with increasing concentrations of the MEK inhibitor trametinib results in a synergistic decrease in viability in uveal melanoma cell line 92.1 (A) and conjunctival melanoma cell line CRMM1 (B). Drug interaction was calculated using BLISS independence score. E-values < 0 indicate synergism.

IV *SAMMSON* inhibition as monotherapy and in combination with MEK inhibition reduces tumor growth *in vivo*

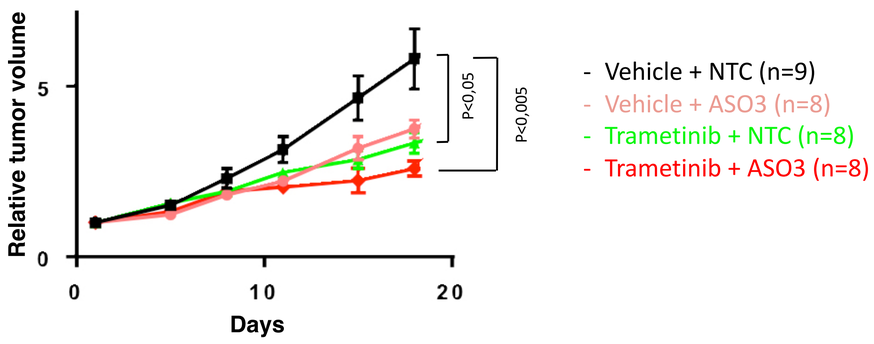


Fig. 6 *SAMMSON* inhibition (ASO3) as a monotherapy inhibits tumor growth. Combining ASO3 with MEK inhibitor trametinib results in a further decrease of the tumor growth.

## CONCLUSION

- *SAMMSON* knockdown results in
  - Reduction in cell viability and induction of apoptosis
  - Decreased mitochondrial respiration
  - Decreased tumor volume *in vivo*
- *SAMMSON* inhibition synergizes with MEK inhibition

## FUTURE DIRECTIVES

- Identification of *SAMMSON* interaction partners
- Validation of the observed phenotype using alternative ASOs
- Combination therapy of *SAMMSON* inhibition with PKC inhibitors

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