XON11, a novel multi-target treatment approach in pancreas cancer

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Abstract 440

XENOTHERA

INTRODUCTION

Pancreatic cancer continues to be one of the most lethal cancer types, with a 5-year overall survival rate of only 12%. It is one of the greatest challenges in oncology, as chemotherapy and immunotherapy have not significantly improved patient outcomes. Therefore, there is an urgent need for new therapeutic approaches.

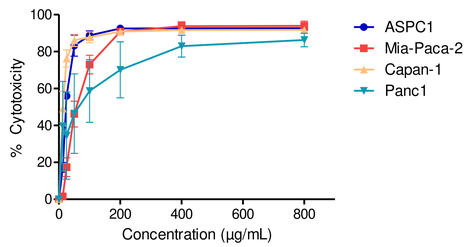
XON11 is a new polyclonal antibody targeting several pancreatic cancer antigens, including KrasG12D. The aim of these studies was to assess the tolerance and efficacy of XON11 in non-clinical pancreatic cancer models.

MATERIAL AND METHODS

- XON11 is obtained by hyperimmunizing rabbits with tumoral antigens
- KRAS mutation in pancreatic adenocarocarcinoma cell lines tested:
  - ASPC1: KRAS G12D
  - Mia-Paca-2: KRAS G12C
  - Capan-1: KRAS G12V
  - Panc1: KRAS G12D
- ***In vitro Assays***
  - Anti-tumor activity was assessed in a panel of pancreatic cell lines in a complement dependent cytotoxicity assay in presence of rabbit complement (1:3) and serial dilution of XON11 after 1h or 24h of incubation.
  - Apoptotic assay was performed on ASPC1 cell line in presence of increased concentrations of XON11 (0, 30, 100 and 300 µg/ml) and labelled with AF488-conjugated Annexin V after 24h of incubation
  - 3D culture of ASPC1 have been developed to study repeated administrations of XON11 and tumorigenicity.
- ***In vivo studies***
  - Xenograft mice models were obtained by subcutaneous injection of 5.10^6 pancreas tumoral cells (ASPC1) in 50% Matrigel to generate a model of pancreatic adenocarcinoma. Treatment was initiated at the onset of tumor growth (approximately 50 mm3) and was performed three time a week. Treatment consisted of intraperitoneal injection of XON11 or Gemcitabine at 40mg/kg. Tumor growth was assessed by measuring tumor volume.

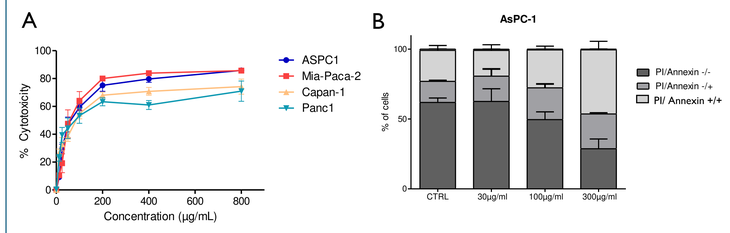
RESULTS

XON11 induces a potent anti tumoral activity against a panel of pancreatic cancer cell lines (CellTiter-Glu 24h)

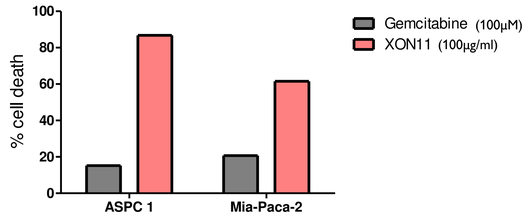


After 24 hours incubation with serial dilutions of XON11 and in the presence of rabbit complement, XON11 induced cytotoxic activity ranging from 70% for the least sensitive cell line to 90% for the other cell lines.

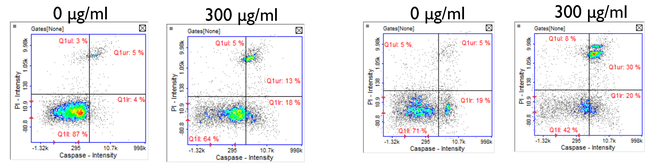
This anti-tumor activity essentially involves **2 main mechanisms of action:** complement dependent cytotoxic activity (graph A below) obtained after 1 hour's incubation in the presence of rabbit complement, and apoptosis (graph B) obtained after 24 hours' incubation with XON11 alone.



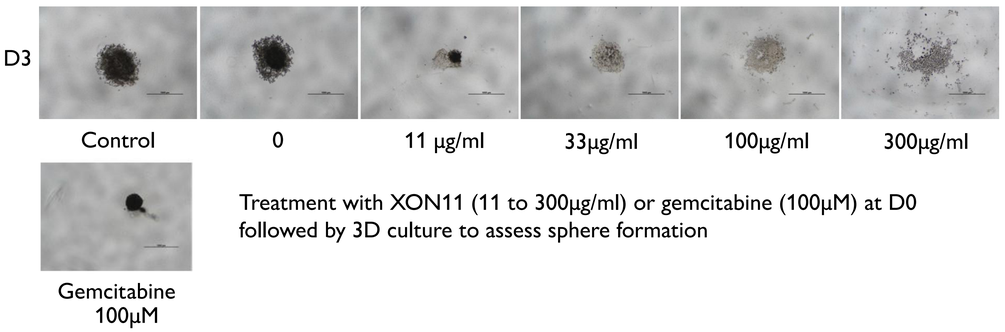
XON11 induces tumor cell death even in pancreatic cell line resistant to gemcitabine



XON11 induces apoptosis via both pathways: intrinsic and extrinsic as shown by Capsases 8 and 9 activations

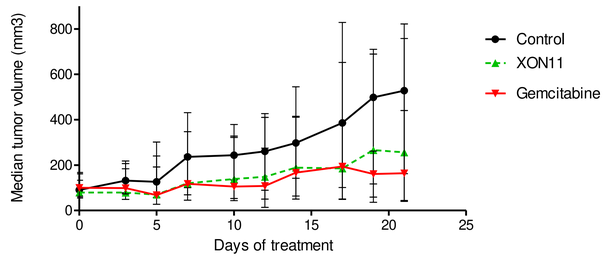


XON11 reduces the tumorogenicity of ASPC1 cells , unlike gemcitabine, by blocking sphere formation



Treatment with XON11 (11 to 300µg/ml) or gemcitabine (100µM) at D0 followed by 3D culture to assess sphere formation

XON11 is effective and well tolerated in ASPC1 xenograft mice model



XON11 reduces tumour growth by more than 50% after 3 weeks of treatment, with no associated toxicity. A 20% mortality rate was observed in the gemcitabine-treated group, demonstrating the toxicity of gemcitabine at this dose.

REFERENCE

To learn more about polyclonal antibodies in oncology:

Ciron et al. JCI Insight 2024 Feb 8;9(3)

Poster high resolution

CONCLUSION

- XON11 displays higher potency against pancreatic cancers compared to Gemcitabine
- XON11 acts via 2 main modes of action: CDC and apoptosis, with activation of both intrinsic and extrinsic pathways
- XON11 reduces the tumorogenicity of pancreas cancer cell line ASPC1, by blocking spheroid formation
- XON11 reduces pancreas tumor growth in xenograft model after 3 weeks of treatment with no associated toxicity

XON11 can provide a novel and promising therapy for fighting recurrent pancreatic cancer

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