Examining the synergistic effect of venoms to enhance chemotherapeutics and irradiation using high content cell imaging

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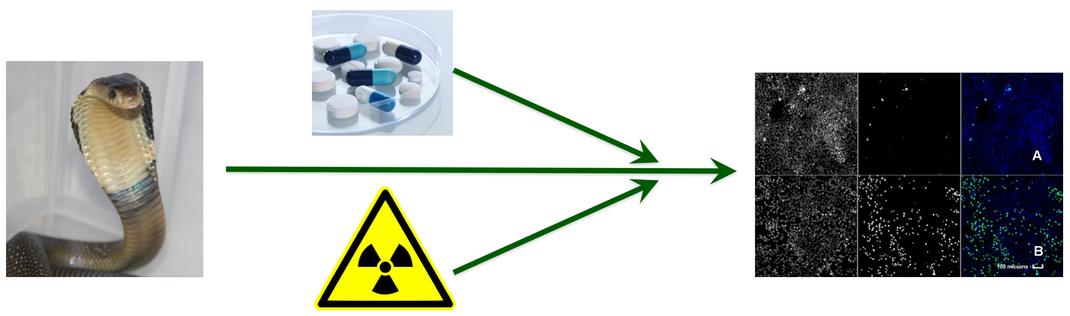
1 Overview

- This study was designed to elucidate potential synergistic effects of venoms and current cancer treatment using phenotypic screening in-vitro
- SKOV3, ovarian cancer cell line, and three glioblastoma (GBM) stem cell lines were used to study effects of treatments and investigational venoms
- Low dose (0.1ng/ml) of some venoms was synergistic with Paclitaxel and modulated patient glioblastoma cell response to irradiation.
- Caspase-3 was activated in combinations where venoms were dosed at 0.1ng/ml suggesting apoptosis rather than necrosis

2 Introduction

- Chemotherapeutics and radiation are key cancer therapies with significant side effects
- Cancer therapy toxicity reduces quality of life and often treatment compliance
- Many venom peptides have selective toxicity to cancer cells in-vitro
- High-content imaging with stained cells (Hoechst 3342 & Draq7) allow for measurement of target agnostic effects of drug action.
- Draq7 is a marker of cell membrane integrity and Caspase-3 activity denotes apoptosis

3 Methods



- SKOV3, ovarian cancer cell line, and three patient derived glioblastoma (GBM) stem cell lines were dosed with 12 phylogenetically diverse venoms from snakes and arachnids
- SKOV3 cells grew as 2D monolayer and GBM cells as 3D spheroids
- All cells were stained with Draq7 and Hoechst 3342 for high content imaging
- Confluent and sub confluent SKOV3 cells were incubated with venoms for 72hrs with and without Etoposide or Paclitaxel
- GBM cells were dosed with venoms in combination with radiation (5 Gy; X-Rad 320, Precision XrayInc., USA)
- Cell number, cytotoxicity, spheroid size and caspase-3 activity were measured using ArrayScan VTI HCS Reader (Cellomics)

4 Results

Figure 1. Venom cytotoxicity is dependant on cell confluence

Echis carinatus, viper | *Naja nigricollis*, elapid | *Hadrurus arizonensis*, scorpion

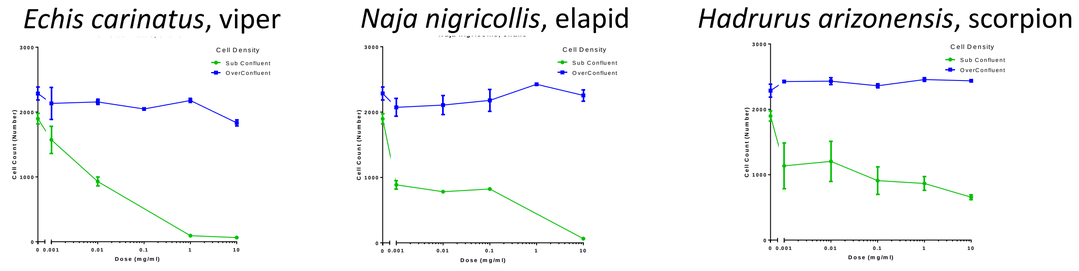


Figure 2. Snake venom, but not scorpion venom, increases Draq7

Echis carinatus, viper | *Naja nigricollis*, elapid | *Hadrurus arizonensis*, scorpion

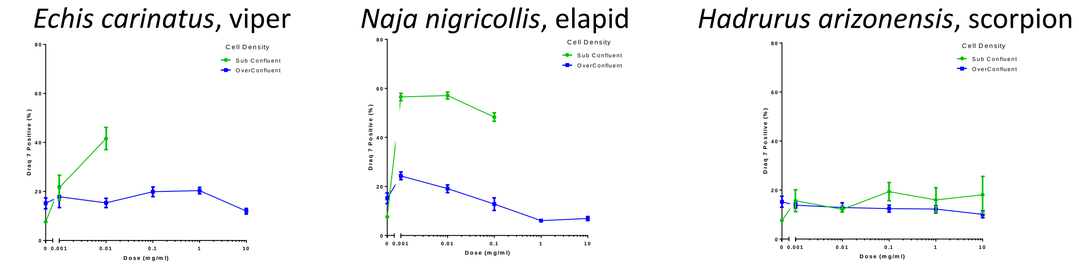


Figure 3. venom synergy with chemotherapeutics

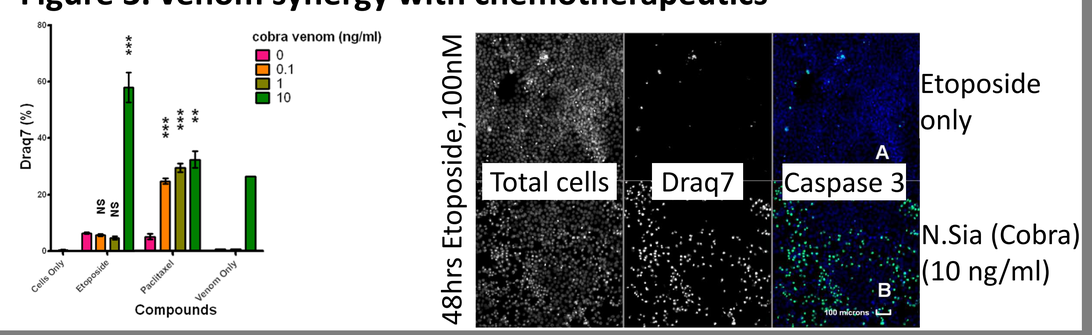
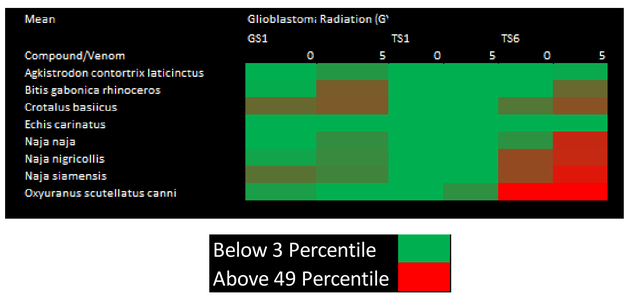


Figure 4. venom effect on GBM irradiation sensitivity



Snake venom at 0.01ng/ml increased sensitivity to irradiation in two of three GBM stem cell lines.
This demonstrates patient variation and may be useful in stratification

5 Conclusions

- Venoms appear to target rapidly dividing cells which is a key mechanism in cancer treatment
- Scorpion venom cytotoxicity does not increase Draq7
- Venoms could contain active peptides that modulate cell responses to chemotherapy and radiotherapy
- Further work is required to elucidate their active components and their drug like properties

12 YEARS ANNIVERSARY

Venomtech

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