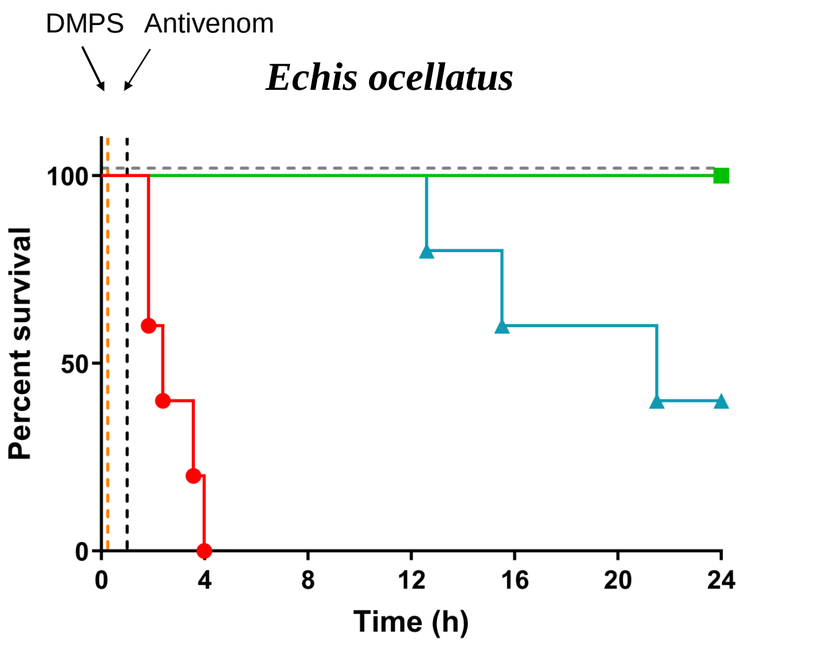
Small molecule toxin inhibitors as rapid pre-hospital interventions for treating snakebite

- Snakebite is characterised by high mortality (138,000 deaths/annum) and morbidity (400,000-500,000 cases/annum)
- 75% of fatalities occur outside of hospital settings
- Antivenom is the only current treatment but comes with several challenges, including: restricted snake species efficacy, poor safety, high cost and a requirement to be delivered in a clinical setting
- There is therefore an urgent need for effective, rapid, safe and affordable field-based interventions for snakebite
- To this end we have begun exploring the potential of small molecule-based toxin inhibitors as new snakebite therapies

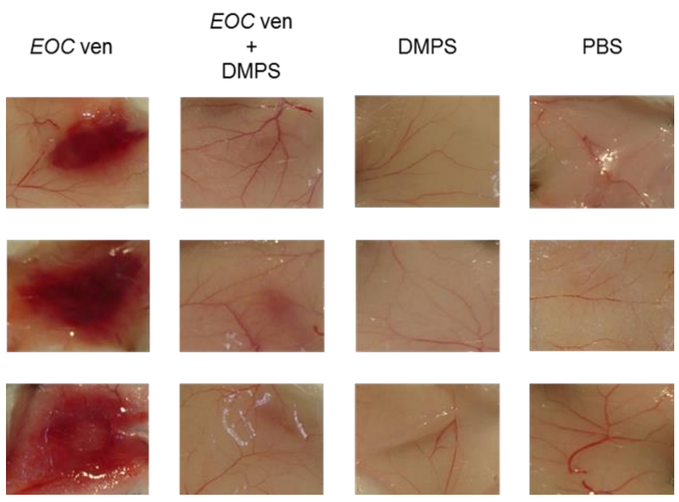
Metal ion chelators

- Target haemotoxic venoms rich in snake venom metalloproteinases (SVMPs)
- SVMPs are zinc-dependent enzymes that are abundant in viper venoms
- The licensed oral metal chelator DMPS (Dimaval) is highly effective pre-clinically against *Echis ocellatus* (saw-scaled viper) venom

Effective against venom lethality



Effective against local haemorrhage

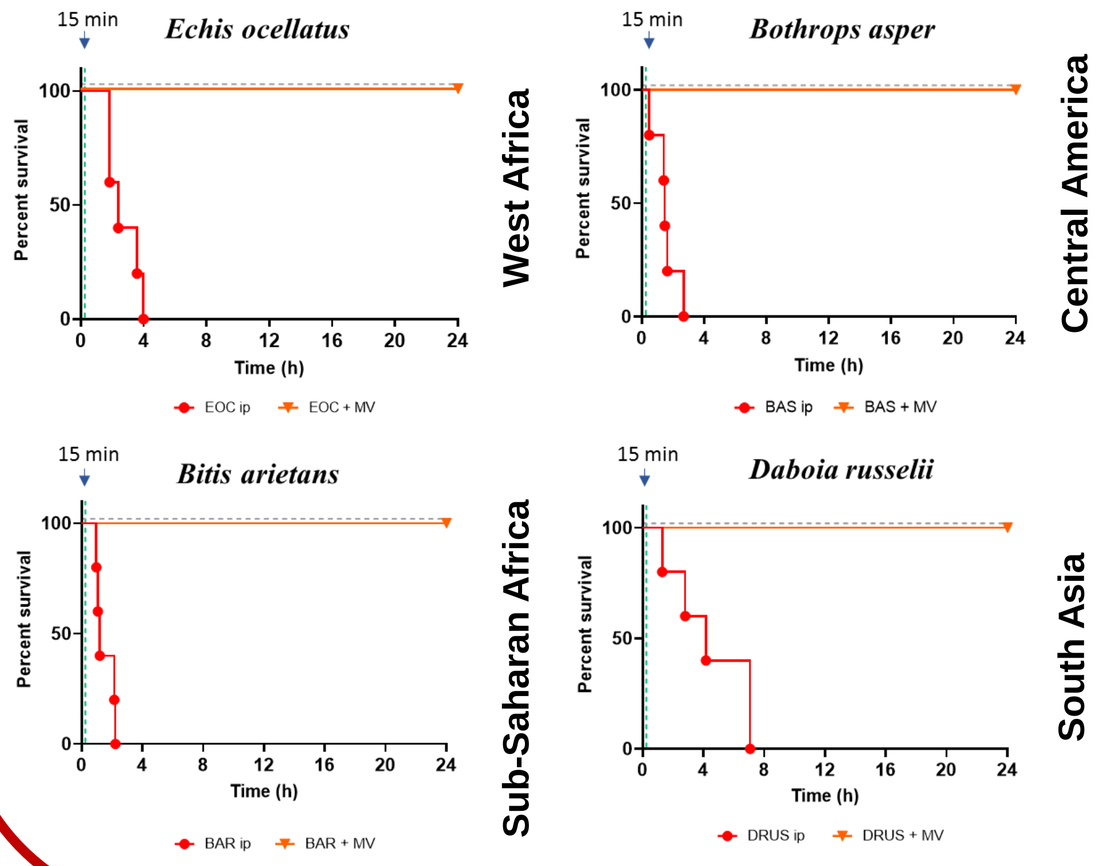


- Oral delivery shows efficacy
- Amenable for use as a rapid field intervention
- Phase 1 clinical trial planned in healthy volunteers in Kenya

Inhibitor mixtures

- Viper venoms display considerable diversity in toxin composition
- Targeting the main enzymatic toxin classes of viper venoms (SVMPs and phospholipases A2 [PLA_2]) with specific inhibitors: marimastat and varespladib

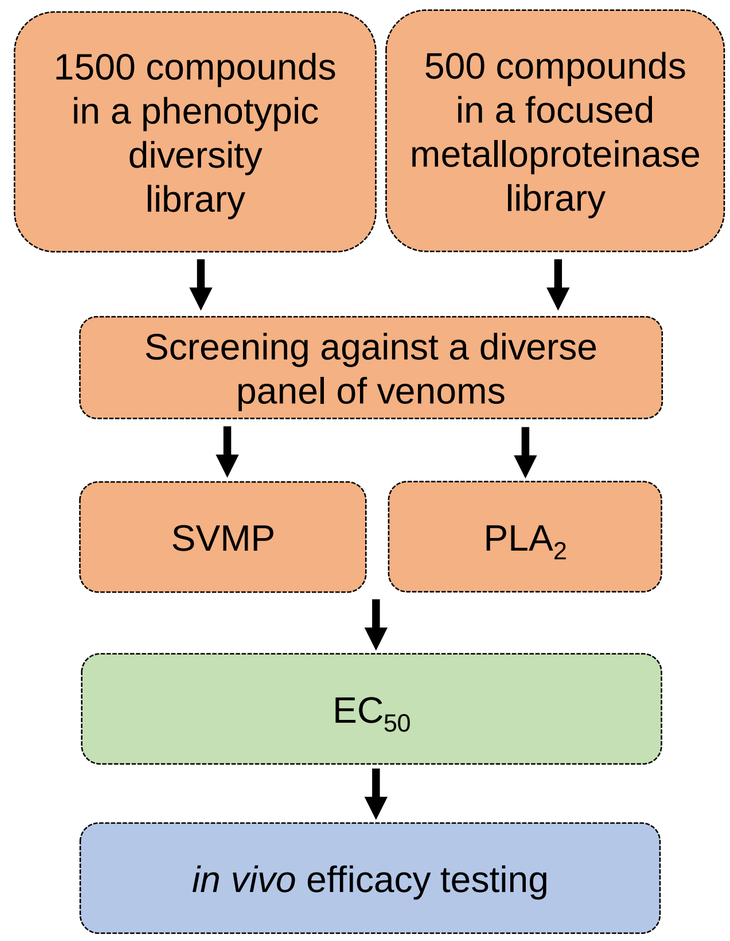
Broadly effective against venom lethality



- A mixture of the two inhibitors prevents lethality by various haemotoxic venoms
- Both drugs have been shown to be safe in prior Phase 1 clinical trials
- Small molecule drug combinations offer much promise as new, cross-specific, snakebite therapies

Drug portfolio expansion

- In-house SVMP and PLA_2 *in vitro* assays are amenable to high throughput screening (HTS) for the discovery of novel inhibitors
- Scale up of these assays has allowed the initiation of a screening campaign in collaboration with Johnson & Johnson to test two small molecule compound libraries



This screening campaign will facilitate:

- Discovery of back-up compounds to the current candidates (see left)
- Discovery of potential novel lead series
- Proof of concept for a successful drug discovery pipeline for use in new screening programmes against other venom toxin targets

CSRI's small molecule portfolio in 2020

Hits	Lead series	Candidates	POC drugs
compound library screening hits		DMPS marimastat varespladib mixture	

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