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 haemotoxically 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

**Inhibitor mixtures**
- Viper venoms display considerable diversity in toxin composition
- Targeting the main enzymatic toxin classes of viper venoms (SVMPs and phospholipases A2 [PLA₂]) with specific inhibitors: marimastat and varespladib

**Drug portfolio expansion**
- In-house SVMP and PLA₂ 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

**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**

**Broadly effective against venom lethality**

- A mixture of the two inhibitors prevents lethality by various haemotoxically 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

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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**

<table>
<thead>
<tr>
<th>Compound library</th>
<th>Screening hits</th>
<th>POC drugs</th>
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<tbody>
<tr>
<td>Antivenom</td>
<td></td>
<td>DMPS</td>
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<tr>
<td>Echis ocellatus</td>
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<td>marimastat</td>
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<td>Varespladib</td>
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Centre for Snakebite Research & Interventions
Liverpool School of Tropical Medicine