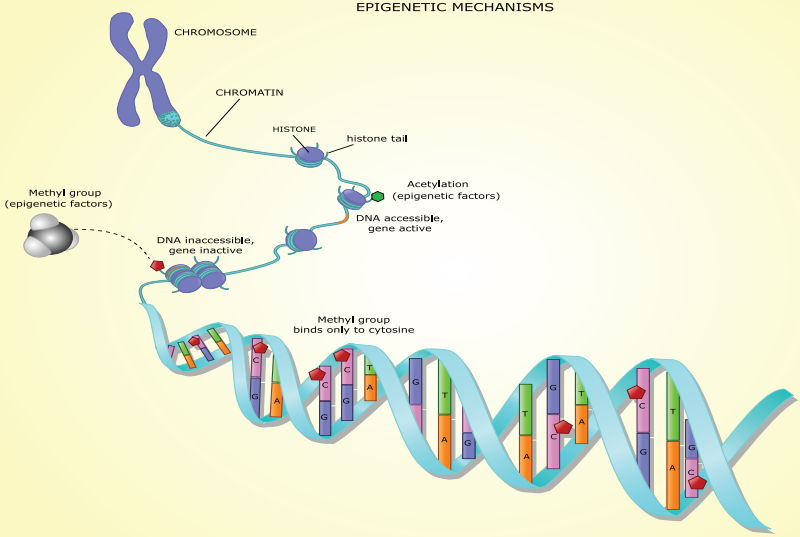
VENOMTECH®
Drug Discovery Solutions™

Epigenetics Targeted Venom Discovery Arrays



Covalent modifications of DNA (e.g. cytosine methylation) or of histone proteins (e.g. lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation) play central roles in many types of epigenetic regulation. Epigenetic factors that produce these modifications can be affected by development (in utero, childhood), environmental chemicals, drug/pharmaceuticals, ageing and diet which in turn can lead to cancer, autoimmune diseases, neurodegenerative disorders and diabetes. Given the large number of epigenetic factors, identifying small molecules and biologics with satisfactory selectivity profiles presents a huge challenge for epigenetic target drug discovery.

Maximize your potential to discover novel epigenetic agents with T-VDA^{Epi} and T-VDA^{Bromo} and T-V*DA*^{KDM}

- Construction
  - ✓ Venom from 12 species; 2D HPLC fractionation
  - ✓ Echo qualified 384 plates; 1-5 peptides / well; 3 replicates per plate
- Delivery lead time
  - ✓ 8 to 10 weeks; plates shipped at ambient temperature
- Follow-up Services
  - ✓ Hit ID, SAR and bulk resupply for pharmacology components supply for pharmacology components

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A proof of concept study to demonstrate binding and inhibition of epigenetic targets by crude venom preparations

- Venomtech 30 venom diversity set was screened in four histone lysine demethylases (KDM) inhibition assays and and three bromodomain displacement assays.
- The venom samples were made up with 20 μl assay buffer (50 mM Hepes (pH 7.5), 0.1 % BSA, 0.01 % Tween 20 so give 2.5 μg/μl). 200 nl was then Echo dispensed into the plates, giving a final assay volume of 10 μl and a final assay concentration of 0.05 μg/μl.
- Bromodomains were assayed using Alphascreen equilibrium binding assays which measure the displacement of a biotinylated peptide from the His tagged protein using streptavidin donor beads and Ni-NTA acceptor beads.

Results

- KDMs – a number of venoms showed inhibition, especially for JMJD2A and JMJD3A with some selectivity over the JARID family of KDMs. A generic chemical inhibitor (2,4,-PDCA) inhibited as expected all targets as expected (Graph 1)

- Bromodomains - a number of venoms show selective displacement of control peptides from the SGC bromodomain proteins, BRPF1B, CECR2A and FALZA, notably, venom 25 which shows selectivity between CECR2A and FALZA (Graph 2)

Figure 1 KDM inhibition

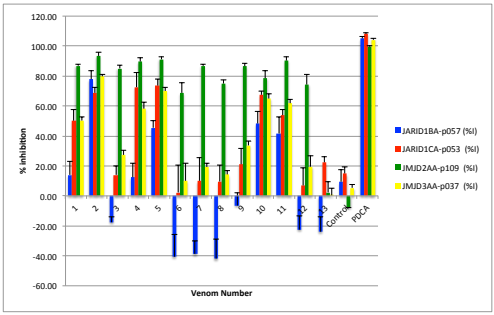
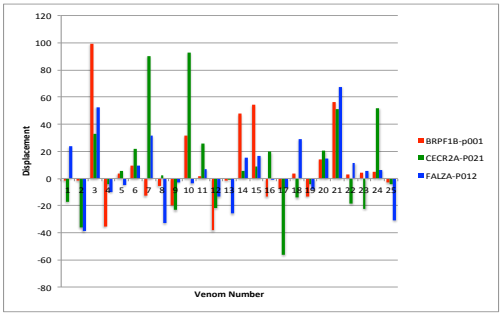


Figure 2 Bromodomain binding



Summary

- Data from this POC study shows that venom components can act directly on epigenetic factors such as bromodomain containing proteins and histone lysine demethylases
- In addition some venoms have shown selective binding /inhibition between different KDMs and between different bromodomains
- This study was conducted using the Venomtech 30 species crude venom diversity set and generated a hit rate of >30%;
    - We expect that tests of 2D fractionated targeted venom arrays on other reader domain groups, writers and erasers will generate novel hits against these targets

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