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Production of Naturally Compressed Screening Arrays

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Abstract
Animal venoms and toxins are a rich source of novel biologics with several making the progression from tool to therapeutic such as FDA approved Integrilin™ (Eptifibatide) (Millennium pharmaceuticals)[1] derived from Rattlesnake venom for unstable angina. Several other animal toxins are in various stages of research for such applications as antimicrobials, analgesics, thrombosis and even cancer; contortrostatin (copper head, *agkistrodon contortrix*, venom) reduces metastasies from breast carcinomas[2]. Venoms are complex mixtures of peptides, enzymes and smaller biomolecules amongst others, thus representing a vast library of tools. Traditional screening methodologies required single compounds in single wells but with the advent of compressed screening plates, much higher density screens can be run with fewer reagents and in shorter time frames. The Venom Discovery Array™ (VDA™) is a naturally compressed hit-to-tool screening plate produced by Venomtech Limited that makes use of natures compressed libraries (venoms) and phylogenetic diversity allowing for maximum discovery potential. These VDA's can be targeted to specific disease areas with many related species or maximum diversity with up to 96 species from a wide group of animals including snakes, spiders, scorpions and insects. (1) Philips and Scarborough, (1997), The American Journal of Cardiology 80(4): 11-20. (2) Mohit Trikha, Yves A. De Clerck, and Francis S. Markland, (1994) Cancer research. 54:4993-4998.

Method
Initial phylogenetic data was collected from multiple sources to understand the taxonomic organisation within the suborder - Serpentes (snakes) and the class - Arachnida (spiders and scorpions) as these were indentified as key groups of venomous animals of most use to biologicals discovery and therefore to produce the Venom Discovery Array (VDA) from. We then purchased animals from as many subgroups as possible to represent the maximum diversity. The VDA Serpentes contains venom from 32 species in triplicate, these are representatives from six subfamilies and three families (Viperidae, Elapidae and Colubridae). The VDA Mygalomorphae is made of venom from 48 species in duplicate, covering ten subspecies of the Theraphosidae family with two representatives from the Nemesiidae family. The third standard array contains the most diverse collection of venoms – VDA Arthropoda. This array of venom from 96 species contains all those from the VDA Mygalomorphae alongside true spider venoms (seven sub families), scorpion venom (six families), with centipedes (Scolopendriae family) and insects.

All crude (whole) venoms are frozen in low-protein binding vials in 2D barcoded 96-well arrays. Whole venom is used to eliminate any potential losses through lyophilisation and eliminate the need to work with toxic dusts. The venoms can be then diluted into any assay buffer ready for use on many automated platforms.

Venom components
Enzymes
Peptides
Nucleotides
Carbohydrates

Some venom uses
Ion channel modulators
Anti-microbials
Enzymes – Biocatalysts
Haematology
Growth Factors
Anti-cancer

Principle of Naturally compressed array
In order to increase throughput the principle of compression comprises putting multiple compounds in each individual well, and a redundancy such that the same compound appears in several wells thus hits can be deconvoluted. Evolution has provided this very system as a result of natural selection; venoms contain complex mixtures and those from closely related species often share components thus there is redundancy to help identify the hit. In addition natural selection has provided modification to many components which is great substrate for selectivity and potential structure - activity relationships to be determined.
The arrays are produced form species being held onsite means that follow-up is easy as bulk production can be provided from any species of interest from the array.

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