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COMMENTARY

Drug Discovery Benefits from Venomous Clues

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Abstract: Pharmaceutical drug discovery is reliant on innovative research and development approaches that uncover novel agents that could service a drug pipeline. Development of novel drugs to combat human disease is largely dependent on the availability of safe and effective drugs, many of which are under development and evaluation—the so-called "drug pipeline". While the costs involved in novel drug discovery, research, development and clinical evaluation are quite significant, one approach that can prove both cost-effective and a viable source of bio-therapeutic agents involves bio-prospecting for therapeutically active compounds commonly found in natural resources including microorganisms, plants, invertebrates or reptiles. In a recent issue of Proteomic Insights, Hang Fai Kwok et al provide a historical and current perspective of proteomic and genomic approaches on lizard venoms that have allowed us to understand and appreciate not only this valuable resource of discovering biologically active molecules, but also to alert us to the need of conservation of such invaluable and beneficial natural resources.

Keywords: drug discovery, proteomics, bio-prospecting, genomics

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Introduction—Natural Resources in the Age of Modern Drug Discovery

For well over a century, drug discovery has been a rather serendipitous process of screening pre-existing agents for desirable effects against a specific target. On the other hand, drug discovery has also benefited from bio-prospecting natural resources for candidate lead compounds. Such natural resources include plant species, marine invertebrates, microorganisms and certain species of amphibious and non-amphibious reptiles.[1–5] Basic laboratory research applying proteomic and genomic approaches has served to provide new information regarding the molecular and physiological pathways of disease pathogenesis and the health effects of particular drug targets. A drug target (new or pre-existing) can physiologically be considered a cellular or molecular entity (tumor cell, microbe, enzyme, protein, or nucleic acid sequences) that plays a pivotal role in the pathogenesis of a particular disease of interest, and which by itself, is the key focus of a particular drug or agent action.

Traditionally, high-throughput screening approaches using robotic analytical and sampling devices have been used to survey the potentially therapeutically useful repertoire of compounds and agents for action against a particular target. Such screening approaches inform us of the selectivity and specificity of a particular agent for its target. During this screening process, it is hoped that lead drug candidates can be secondarily assessed for structure-activity relationships—a process whereby the specificity and activity of a particular lead compound is modified for optimal activity against the drug target in the absence of undesirable "off-target" effects, as well as enhancing the bioavailability and pharmacokinetic properties of the lead compound, for example the absorption, distribution, metabolism and excretion properties of that compound.

Despite combinatorial chemistry and rational drug design approaches in lead compound drug discovery, the screening process for viable candidate drugs is highly reliant on natural products from such diverse species as plants and certain species of lizard.[4,5] It should be no surprise that viable drug targets for therapeutically targeting infectious diseases, cancer, acute and chronic inflammation as well as cardiovascular disease states, have all benefited from novel drug discovery or semi-synthetic drug analogs derived from natural venom resources. For example, for almost a century, microorganisms have been an invaluable source of anti-microbials and more recently, a plant compound called Paclitaxel or Taxol, was isolated from the Pacific Yew tree (*Taxus brevifolia*), and found to have tumoricidal activity in the settings of breast, lung and ovarian cancer, among others.

Why *Lacerta*?

In the recent review article by Kwok et al,[6] the concept of lizard (Lacerta) venoms as a potential source of biologically active therapeutic agents is critically surveyed. The review article discusses advances that have been made over the last several years in the development of minimally invasive procedures for harvesting lizard venoms. Molecular biology approaches for designing cDNA libraries of critical utility, proteomic and genomic approaches for identifying putative therapeutic drugs in lyophilized lizard venoms and the identification of novel venom toxins are also discussed with particular emphasis on the discovery of several novel toxins and inhibitory peptides including helokinestatins (a bradykinin-receptor-mediated inhibitory peptide) and natriuretic peptide toxins in the venoms of such diverse lizard species as helodermatids and varanids.

The authors survey the proteomic and genomic studies conducted on lizard venoms, but the questions that are borne in mind are: why *Lacerta?* And why bother? The answer rests in the rapidly advancing field of functional toxico-genomics and proteomics and the mining of the derived data for novel research-orientated and therapeutically useful compounds in lizard venom without the need to sacrifice the life of the animal. The authors make the case from several seminal studies by Kwok et al[7,8] that from one sample of lizard venom, it is possible to derive complex but complementary data with regard to transcriptome, proteome and genome that can all be applied to scientific and drug discovery applications. Since a modified technique had been developed for the efficient recovery of lizard venom,[9,10] a technique for the non-traumatic and repeated harvesting of lizard venoms for drug discovery and scientific research applications had been standardized. This also serves to preserve the life of many species of lizards that are considered at risk or high risk of extinction or are considered rare or protected species.

The helodermatid lizards are considered one of the most important species of lizards that have attracted increasing attention because of the broad utility of their venoms for biomedical applications.[6] Kwok et al describe how the venoms collected from the helodermatid lizards have permitted discovery of novel bioactive agents such as the exendin peptide toxin (sold over the counter as Byetta™) for the treatment of diabetes.[6,11] Remarkably, Kwok et al discovered a novel bradykinin-receptor inhibitory peptide from the venom of helodermatid lizards which was named helokinestatin.[10] Clearly, this remains an evolving field of scientific and drug discovery where Kwok and others[10,12] have pioneered the way forward for novel drug discovery in lizard venoms.

Conclusion

Kwok et al remind us of an under-appreciated, richly diverse and sustainable resource for novel drug discovery in the management of human disease. Such discovery has clearly benefited from the "Omics" revolution and the ability to survey extensive proteomic and genomic data sets for novel drug discovery and drug targets. The application of "Omics" approaches to candidate drug discovery will clearly lend itself to more cost-effective and bioprocess efficient means of drug discovery from naturally available biotherapeutic agents including those found in the venoms of *Lacerta*. Not only does such research provide important evolutionary clues of the diverse nature of lizard venoms, but also provides important new leads on the discovery of novel classes of biotherapeutic drugs in a field where new drugs are urgently needed for newly emerging diseases and drug targets. In the following 10 years, there is no doubt that such research approaches will yield additional information on novel classes of therapeutic drug discovery and evolutionary insights of the complex nature of lizard venoms.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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