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editorial

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Natural products as lead-structures: a role for biotechnology

Natural products play a key role in healthcare and pharma research, as many medicines are either natural products or derivatives thereof. It is estimated that about 40% of all medicines are either natural products or their semisynthetic derivatives [1]. This may not be surprising as herbal medicine has been a tradition of healthcare since ancient times and natural-extracts screening has been one of the roots of pharma research, where penicillin, erythromycin and rifampicin (bacterial infections), statins (cholesterol lowering/hyperlipidemia), quinine and artimesinin (malaria), paclitaxel, vinblastin and vincristin (cancer), salicylic acid and nonaddictive cocaine derivatives (pain relief), are a few well-known natural product-based medicines. For bacterial infections, about 80% of the medicines in clinical use, are either natural products or their derivatives, while about 60% of all anti-cancer agents are either natural products or derivatives thereof [1,2].

Natural products were developed by microorganisms, plants, marine organisms, amphibians and animals for several purposes including, as building blocks, coenzymes and cofactors, for host-defence against microbial infection and predators (animals), protection of their ecological niche, communication between and within species, pigments, cellular signaling and gene-expression, and homeostasis of organisms. As a consequence of the duplication, conservation and evolution of genes across the animal kingdom, natural products exhibit pharmacological activities over a range of indications among mammalian species, including humans. Some examples include the anti-fungal agents (a) cyclosporine, which is an inhibitor of cyclophilin and is used as an immuno-suppressant in humans, and (b) statins, which are inhibitors of HMGCoA reductases and are used as cholesterol-lowering agents in humans.

Some of the constraints of natural products as lead structures are known and have been addressed. These include automated fractionation of complex mixtures into simpler fractions for high throughput screening, purification and dereplication, determination of 3D-structures, and developments in the total synthesis of natural products and natural product-like libraries [1–7]. Some limitations do remain, including the isolation of certain natural products in large amounts, total synthesis by chemical approaches, or limited scope for chemical modification. Also, less than 10% of all plant species, marine organisms and microorganisms have been screened for biological–pharmacological activity. The loss of plant species and habitats through environmental change is a concern, while agriculture may be a limitation in some cases when yields are low or when growth periods are long and large-scale harvesting of medicinal plants from forests may affect the forest ecology. Some species are difficult to cultivate under laboratory conditions as cell- or tissue-cultures, while large-scale fermentation is sometimes a constraint. These and other limitations suggest that a range of unique scaffolds and pharmacophores are currently out of reach for pharmaceutical research.

It is of interest to support and emphasize an area of natural product-based lead discovery based on biotechnology, namely genomics and the identification of biosynthetic pathways of natural products. Advances in genomics enable the isolation of genes for secondary metabolite biosynthesis from a range of species, including microorganisms, marine organisms and plants. This

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.02.008

would strengthen several areas of natural product-based lead discovery, including (a) heterologous expression and over-production of natural products to overcome limitations in natural sources and total chemical synthesis, (b) isolation of intermediates and unique scaffolds in these biosynthetic pathways for chemical modification and natural product-like library synthesis, (c) isolation of homologous genes and their cognate gene clusters from organisms that are otherwise difficult to access or cultivate for screening, (d) identification of new biosynthetic pathways for novel natural products, (e) semisynthesis of new derivatives of known natural product-based drugs with a modified pharmacological profile.

When drugs are obtained from natural sources, these sources may be depleted, for example, plant species, marine organisms. Some potent natural products may be moderately toxic for the producing species, and hence produced only in low amounts. The capability to over-produce natural products through heterologous expression in microbial or plant cell culture, may bypass these limitations [8–10].

Heterologous biosynthesis of natural products in microbial or plant cell culture would enable the isolation of intermediates in these pathways, which could serve as novel scaffolds for the semisynthesis of natural product-like libraries. This would be relevant when the intermediate-scaffold is novel and not amenable to total chemical synthesis. This would be of special significance when chemical modification of the natural product leads to an enhanced or modified pharmacological profile. This approach would be relevant for modifying natural products that are cytotoxic for mammals, into semisynthetic, potent, selective and efficacious anti-infective agents for tropical diseases [11,12]. Given the genetic differences between parasites and mammals, and the genetic variation among parasites of tropical diseases, the scope of this approach to develop anti-infective agents against several tropical diseases, with a few cytotoxic natural products as templates, deserves special emphasis and support. Given the need for new medicines to treat tropical diseases, this approach would be of special significance. This approach would be relevant for other indications, when the differences between homologous drug-targets are significant, or when the pharmacological profile of a natural product needs to be enhanced [17].

Advances in the genomics of natural product biosynthesis would enable the identification of genes for secondary metabolite biosynthesis from a range of species, including microorganisms, marine organisms and plants. Patterns will emerge, as some enzymatic steps are common to several secondary metabolite pathways, and the corresponding genes may be conserved across a range of species. As the genes for secondary metabolite pathways are organized as gene clusters, this may be a way for identifying novel gene clusters from various organisms, based on gene-homology and genome-mining [13–16]. This may be more efficient than a brute force genomics approach and may be relevant for organisms that are difficult to cultivate under laboratory conditions, and where repeated bio-prospecting has constraints. This may suggest that the elucidation of the genes and biosynthetic pathways of natural products is an important area of research that would require adequate support. On a cautionary note, it may be mentioned that the discovery of natural products with pharmacological activity has (so far) always preceded the use of biotechnology, wherein the latter approach is applicable when a single chemical entity has the required pharmacological effect.

The complete repertoire of natural products has not been fully explored for natural products screening and lead discovery. This is relevant for natural products from organisms that are difficult to bio-prospect or cultivate *in vitro*. The capability to isolate gene clusters for natural product biosynthesis from such organisms and clone these into heterologous hosts for over-production under laboratory conditions could broaden the scope of natural product-based lead discovery. In addition to this further research is needed to develop ways of achieving high production strains of some natural products in heterologous hosts. Given the role and potential of natural products as lead structures, and the unique biochemical transformations that Nature has developed for their biosynthesis, the elucidation of the corresponding biochemical pathways and genes clusters remains an important area of basic and applied research. This article supports the importance of biotechnological approaches for natural product research, as an additional approach in strengthening the scope and success of natural product-based drug discovery, in several indications.

Acknowledgements

The author thanks his former colleagues for discussions on natural products chemistry and drug discovery. The author thanks several botanical research institutes in South India for their courtesy during his visits.

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