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Guest Editorial

Natural Products Regain Attention in Oncology

Cancer is a dreadful disease caused by abnormal and uncontrolled cell division. About 6 million new incidences of cancer are reported yearly worldwide. Nature has given man a variety of useful sources of remedies to cure a number of diseases. Since *ca* 1500, natural products (NP; here the term is restricted to small-molecule secondary metabolites) have played a significant role in drug discovery and development, especially agents active against cancer and infectious diseases [1].

An analysis of new and approved drugs for cancer by the United States Food and Drug Administration (FDA) over the period 1981 - 2002 showed that 62 % of cancer drugs were of natural origin. Natural compounds possess highly diverse and complex molecular structures, compared to synthetic small-molecule drugs, and often provide highly specific biological activities that are likely derived from their rigidity and high number of chiral centres.

Since the discovery of novel anticancer agents – doxorubicin and mitomycin in 1961, and bleomycin and vincristine in 1969 [2] - natural products have been the cornerstone of cancer treatment. However, since the late 1990s, with the rapid expansion of the use of monoclonal antibodies and synthetic protein (peptide) kinase inhibitors against cancer cells, anticancer natural products fell out of favour in the pharmaceutical industry. This situation did not change much until 2007. However, with the approval of three new drugs derived from microorganisms, including alvespimycin and salinosporamide [3] and the new formulations of known natural product-derived drugs (nanoparticle formulations, for example), there has been a wave of renewed interest in natural products in oncology. The recent approval of the microtubule-targeted epothilone derivative, ixabepilone (Ixempra®); the DNA-alkylating marine alkaloid, trabectedin (Yondelis®) and the mTOR protein kinase inhibitor, temsirolimus (Torisel®) is emblematic of the evolution in this area which combines the well-established findings of conventional cytotoxic agents and emerging molecularly-targeted therapeutics. The aforementioned examples also highlight the increasing significance of microbial sources for the discovery of natural-product drugs, although novel molecules of marine and terrestrial origins are regularly approved for the treatment of cancer.

'Bioassay-guided fractionation and isolation' is still a gold standard for the discovery of natural product anticancer agents, which depends mainly on the quality of the NP library with structural diversity, as well as the well-defined cancer-specific molecular targets and bioassay systems set up to monitor the compounds of interest. Not all molecular targets are well adapted to the identification of active NPs. For example, the initial screening of natural extracts against purified protein kinases is generally difficult due to a higher rate of false positives compared to synthetic chemical libraries, and this is caused primarily by non-specific interaction with accompanying interfering compounds, such as polyphenols and tannin, which are

commonly present in all plant extracts. Cell-based assays are more suitable for screening NP extracts [4]. The development of highly robust and sensitive high throughput screening (HTS) assays is a key to minimising expenditures on NP anticancer drug discovery.

It can be envisioned that conventional cytotoxic anticancer agents will still remain the favorites of oncology clinicians, but with a preference for NP anticancer drugs targeting areas other than the tubulin/microtubulin network or the DNA replication machinery. It is expected that increasing numbers of anticancer natural products from plants, marine and microorganisms with desirable efficacy and side-effect profiles will be discovered in years to come. With advances in cell and molecular biology, detailed understanding of the mechanisms of action of NP anticancer drugs will, in turn, aid research in cancer biology and oncology, with these active natural products serving as 'bio-probes' through an approach known as *chemical biology* or *chemical genetics* [5].

References

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