

## Natural Products: Back to the Future in Drug Discovery

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### Editorial

Nature offers an endless pool of unique molecular frameworks with desirable drug-like properties, rendering them ideal starting points for the development of pharmaceuticals [1]. In fact, the history of natural products (NPs) in drug discovery has been extraordinarily successful over the past century, highlighted by prominent examples as the antitumor agents taxol, vinblastine or doxorubicin, the immunosuppressant's for organ transplants cyclosporine and rapamycin, or the cholesterol-lowering agents statins, the top-selling drugs today. Despite this glorious past, trends in pharmaceutical industry moved in the early 90's towards high-throughput screening (HTS) of synthetic compound libraries, coinciding with the premiere of *Back to the Future*, the science-fiction adventure film directed by Robert Zemeckis and starred by Michael J. Fox (\$380 million worldwide in a year) [2]. Owing to the continual pressure within the market to find 'blockbuster drugs' and dazzled by the novel breakneck assay speed of combinatorial synthetic chemistry, most of firms cut back their programs of natural product drug discovery. The main argument against doing further screening of natural sources was related to the incompatibility with HTS analysis, based on issues such as 1) high structural complexity which slows the identification process and makes challenging further chemical modifications, 2) slow production of the target compound into a complex extract which demands labor-intensive purification steps, 3) lack of efficient dereplication methodologies which leads in some cases to rediscovery known compounds.

Over time and despite of massive investment and millions of pure synthetic compounds screened, the initial expectations of synthetic medicinal chemistry were not met, the number of new drug approvals decreasing year by year. Thus, synthetic libraries yielded a "hit rate" of <0.001%, significantly lower than the 0.3% hit rate obtained in the same period for the family of polyketide metabolites (20 commercial drugs from just over 7000 known structures) [3]. Despite this unfavorable context, natural sources have continued delivering successful entities, a total of 19 natural products-based drugs being approved for marketing worldwide in the period from 2005 to 2010: 7 NPs, 10 semi-synthetic NPs and 2 NP-derived drugs [1]. Besides, the recent innovative approaches for screening living organisms as well as advances in emerging areas such as chemical biology or enzyme catalysis have fueled the idea of an imminent second youth for natural products in drug discovery.

Aimed at the first drawback pointed above, recent technological advances include automated coupling of HPLC and MS spectrometry which facilitates identification of chemical entities as well as NMR cryoprobes with extraordinary sensitivity requiring only a few micrograms in carbon correlation spectra. Regarding the generation of novel analogs, this was traditionally a challenging task due to the chemical fragility (sensitivity to pH, heat, metal ions, light, acid or basic media, etc.), structural complexity and functional diversity of NPs. Nowadays, the toolbox of synthetic chemists and biologists has been extraordinarily expanded with the aid of biocatalysis and combinatorial biosynthesis. Enzymes can circumvent most of the aforementioned problems as they exhibit high selectivity and operate under mild conditions in both aqueous and organic media. As a result,

a biocatalytic approach could hypothetically reduce the number of protection/deprotection steps and introduce structural diversity inaccessible via conventional chemical synthesis [4]. Additionally, molecular biology has afforded a new dimension to biocatalysis; engineering natural-product biosynthetic pathways, redefined as combinatorial biosynthesis, allows the isolation, identification and over-expression of any naturally occurring enzyme in a specific host and the use of the recombinant enzyme for a particular transformation. These "biosynthetic enzymes" have already been used as biocatalysts in acylation, glycosylation, macrocyclization and carbon-carbon bond formation reactions, leading to novel analogs inaccessible by chemical synthesis [5]. This fact is especially relevant as only 6% of the 1024 new molecules approved in the past three decades, are directly isolated NPs. In contrast, over half these molecules (57%) are either NP derivatives obtained by semi-synthetic approaches or NP-derived drugs [6].

Regarding the issue of low yield of the target compound in natural extracts, the genetic approach also allows the development of improved production strains, for example, by moving the entire biosynthetic gene cluster to a better expressing host organism. Additionally, both fermentation and purification techniques have experienced major developments in recent years and the novel analytical tools are focused on the automation of the extract preparation, fractionation into partially or fully purified components by HPLC and collection on HTS plates for further bioassay analysis [7].

Dereplication, the identification of known compounds in a complex mixture is essential to speed up drug discovery. In the last years, the analysis of complex natural matrices has become easier thanks to advances in analytical equipments and better compound databases. Some innovative approaches are LC-DAD-TOFMS (liquid chromatography with UV/VIS diode array detection and ESI+/ESI-time-of-flight MS for the assignment of molecular entities) [8] or HPLC bioactivity profiling/microtiter plate technique in conjunction with capillary probe NMR instrumentation, demanding exclusively microgram quantities of extract [9].

The bizarre and sophisticated chemical structures of NPs are the result of an on-going combinatorial chemistry performed by living organisms over millions of years, providing them multiple advantages related to their growth and survival. This explains the unique ability of these entities to specifically interact with biological target molecules.

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Nowadays, despite the extensive searching, it is believed that up to 99% of microorganisms have yet to be discovered [10]. Taking the currently high medical need in therapeutic areas such as oncology or the impact of some diseases in the Third World into account, the dispense of NPs is a luxury we cannot afford. Almost three decades later and after two sequels, the Fourth Part of Back to the Future is coming next autumn. .. With the help of innovative tools, are NPs researches also planning a 'back to the future' with a plethora of novel blockbusters?

In current times, the development of initiatives based on Open-Access journals such as OMICS Publishing Group is essential to break down barriers in the communication of science. I truly believe that "Biochemistry & Pharmacology: Open Access" from OMICS Publishing Group will be an excellent platform for disclosing and discussing recent and future findings derived from the revival of research areas involved in natural products drug discovery.

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