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Letter to the Editors

NATURAL PRODUCTS DISCOVERY: CAVEATS, CONSIDERATIONS, COLLABORATION, CREATIVY AND CONTEMPORARY TECHNOLOGY

Dear editors,

There exists an enormous global need for new, safe, and effective drugs for a broad range of chronic and acute diseases. Most of these exigencies will not be met by “big Pharma”, ever. Consequently, in many countries, for a healthier and more productive population this pharmaceutical “chasm” must be bridged through alternative discovery efforts. At a time when environmental consciousness is increasing, and oil and coal processing for solvents and chemicals will likely be diminished in the future, synthetic pharmaceuticals cannot be relied on to serve as that bridge for the long-term. Natural products have continued to be a steady source of pharmaceuticals in the past 30 years (Newman & Cragg, 2020). However, a more emphatic, structured, and sustainable return to nature, using the contemporary technologies now available, is by far the best option to address global needs (Daley et al., 2021). This brief letter offers some general thoughts on natural product drug discovery programs and their initiation, operation, and development. It is not an exhaustive assessment, neither are the issues raised fully discussed, thus only a few key references are cited. The intention is to offer a background framework for scientists interested in this vast area of natural product research as they consider conducting their programs and publishing in this new and exciting journal. Five general areas of research development are presented: Caveats, Considerations, Collaborations, Creativity, and Contemporary Technology.

A. CAVEATS

i) The discovery and development of a drug, even to the stage of licensing, typically takes several years and considerable investment. Are the resources available to support that intended discovery pathway commitment? Do you have that level of personal persistence? Are there alternative pathways for consideration and approval which would bring drugs to the patient in a shorter, cheaper timeframe, while also maintaining safety and efficacy?

ii) Broad-based drug discovery from natural sources is always a series of compromises based on financial support for information systems, taxonomy, chemistry, and biology.

iii) Extensive background research is needed before a niche program can be developed to avoid wasteful duplicative studies.

iv) Is your research program based on a one-off study of an organism or part of a larger screening program? The intentions and therefore the strategies are completely different.

v) A significant number of compounds with a diverse taxonomic distribution are known to have a wide range of biological activities and may give false positive biological responses. These are IMPS and PAINS and must be identified early in the discovery process to avoid squandering isolation resources (Baell, 2016; Bisson et al., 2016).

vi) Artificial intelligence (AI)-assisted dereplication can identify these interfering compounds, along with other known bioactives, for a particular bioassay. An informatics-chemo-bioassay-linked system is an essential component for initial resource assessments in a drug discovery program.

vii) Marine and terrestrial organisms are typically intimately associated with pathogenic microorganisms, which themselves produce a range of potent metabolites. These may interfere in assay assessment by giving a non-reproducible false positive result, based on collection locale, or they may constitute a “hit” themselves.

B. CONSIDERATIONS

i) Awareness of both short and potentially long-term sustainable sourcing of research materials is essential. Avoid plant bark and slow generating roots for extraction. In laboratory practices minimize the application of heat and non-reusable solvent mixtures. Chromatographic supplies and glassware usage should be minimized. Consider additive manufacturing as a pathway to generate purpose-driven extraction and reagent vessels.

iii) Patenting considerations may push priorities towards new bioactive compounds. “Old” compounds with strong, selective, new bioactivities may, based on prior safety assessments, offer a significant advantage to new compounds in the IND approval process.

iv) Purified metabolites and partially processed extracts of sustainable resources are precious. Think small for sample size testing. Think large for test sample accumulation (collaborate locally and regionally to develop these assets), and for the breadth of bioassays applied to a given sample.

v) New research directions may require new methods. Training of personnel may be necessary for instrumentation and for bioassays.

vi) Geography matters. The same plant from the same location will likely have a modulated metabolic profile in a different season and/or from a different locale. If large compound samples are needed, a strategy for metabolite sustainability is necessary. Climate change in the location of origin will affect metabolic profile, requiring metabolomics and molecular networking studies as integral to the program.

vii) As a taxonomist know accurately what organism is being acquired and processed. As a chemist know precisely (profile and purity) what is being sent for biological assessment, and as a biologist know, at the time of the test, what is being evaluated.

viii) You will not have discovered the cure for cancer or diabetes. Do not suggest that based on one or two assays you have a potential therapeutic agent. Be hypercritical of relative activity and how the biological data are presented in a comparative manner.

C. COLLABORATIONS

i) Drug discovery programs, even limited ones, require collaboration between several disciplines. Quality, intensity, reliability, and consistency are necessary for success.

ii) Before starting, the research collaborations should be supported by negotiated agreements for sharing of intellectual property rights (IPR), compensation strategies for resources access, and authorship of publications.

iii) Based on the countries of sample acquisition, the IPR issues must be negotiated, and local approvals obtained. Time should be allowed for this essential phase in program development

iv) A compound of biological interest should be protected by the institution and then licensed depending on the intended application globally. Think open access for future development in different locations.

D. CREATIVITY

i) Robust, cheap, sensitive, rapid assays that target new mechanisms and approaches are continuously needed. Care is needed in selecting the appropriate positive control.

ii) Discovery includes studies potentiating synergistic relationships, and adjuvants which can deter destructive metabolic, or transport processes related to drug resistance.

iii) Research techniques for discovery are changing rapidly. Continuous program assessment is essential. If you are doing the same science as 5 years ago, something is fundamentally wrong. Know when to stop a program, or aspects of it, to protect resources.

iv) Opportunity may arise from unexpected results; stay aware for the serendipitous outcome.

v) Translation of research has been transformed in the recent past, and even more so with COVID-19 research. The traditional avenues of peer review and publication are changing. Where, how, and when results are published or protected is a collaborative discussion.

E. CONTEMPORARY TECHNOLOGY

i) Every researcher has intimate access to comprehensive information systems and to highly specialized databases. How these assets are used creatively determines the relevance, the focus, and the success of the program. Innovative discovery programs will evolve through integrating the technologies embodied in the Fourth Industrial Revolution and fostering collaborations with the government and industry to address program needs. Considering the relevant sustainable development goals and creating a balance between machine learning, in silico metabolite suggestions, robotic processing of extracts, network pharmacology, and the human interpretation of AI-generated outcomes, are critical elements of an integrated discovery program.

ii) Secure and immutable research data recording is essential, particularly if intellectual property rights and potential patent claims are to be protected.

iii) Where is the primary discovery of an organism of interest being made? Is it in the laboratory or in the field ("ecopharmacognosy in a suitcase")? Microfluidic biosensors for discovery of extracts to be pursued for in-field and in-laboratory use are an important asset for program enhancement.

iv) The ability to define diverse, "silent" biosynthetic gene clusters in fungal and bacterial genomes stimulates their activation as discovery havens for illuminating new ranges of metabolites.

v) Applications of synthetic biology abound for natural product discovery programs, notably for enhancing structure diversity through new operon construction, optimizing biosynthetic pathways, discerning drug targets, and disclosing new enzymes for processes that are chemically and energetically non-sustainable, or use expensive, non-recyclable reagents.

The many ways forward for natural products in drug discovery are clear and the opportunities for creative and meaningful discoveries abundant. Crucial for progress for the patient is high level, focused, dedicated collaborative programs which realize that success involves government, industry, and academia coming together. Territories and egos must be set aside in support of research towards common human health goals of Quality, Safety, Efficacy, Consistency, and Accessibility (QSECA) for nature-derived medicinal agents to meet local and global needs (Cordell, 2019).

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