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COMMENTARY: REFLECTIONS ON 40 YEARS

Chemical Ecology in the Post Genomics Era

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Forty years of the Journal of Chemical Ecology are an important achievement for natural science and also open up a potential, but perhaps unforeseen, expansion of the area. For the future, not only is chemical ecology demonstrating an ability to incorporate and exploit new scientific opportunities from the technologies associated with molecular genetics, but it is also capable of solving problems of these technologies where some new scientific approaches lack rigor, and where bioinformatics alone founder.

The spectacular use of analytical chemistry, combined with electrophysiology and other bioassays to identify minute amounts of highly active pheromones and other semiochemicals throughout those 40 years, stemmed from the central tenet of chemical ecology: the need to account for a biological phenomenon by understanding mediation of chemistry. Quantitative studies comparing activities of synthetic chemicals at similar physiological levels to those in original natural materials demonstrated the validity of claims for having identified the causative semiochemicals. This principle must now be applied to the plethora of studies that use synthetic compounds to perturb natural systems, and particularly gene expression. Without consideration of dose in relation to natural physiology, little can be learned.

Identification of purportedly active natural products has possibly been the most dangerous aspect of current science, suffering from the absence of the rigors normally applied in chemical ecology. We must, however, concede that these rigors can be adopted without the term "chemical ecology" necessarily being used. Thus, we need to ensure that chemical compound identity is not assumed merely by comparison with spectroscopic databases, as is common particularly in high impact generic science publications. The biological component of chemical ecology is widely ignored when no "cause and effect" is determined. Pioneering work by the founders of our subject have sought, with utmost rigour, to identify absolute stereochemistry of semiochemicals by unambiguous synthesis and chiral analytical techniques, often overlooked in other rapidly moving areas of science—to their cost—with even the stereochemistry of the molecular structure of DNA lost when shoddy use of printing processes is not checked for chemical accuracy. In chemical ecology, it is well known that unnatural enantiomers of semiochemicals can exhibit similar, reversed, or no activity, and thereby offer an approach to validation of *in vitro* biological receptor or other systems with which the semiochemical is claimed to interact. Certainly, we in chemical ecology do not miss the importance of positional or geometric isomer designation, with even this being a problem in current publications beyond our subject. These aspects often are so entirely overlooked in recent studies on bioactives, with referees and editors concerned too much with seemingly grand outcomes, that sophisticated recognition processes are missed. As a consequence, misleading new chapters on understanding the interactions between small lipophilic molecules (SLMs), whether semiochemicals or not, and the biological processes they signal and mediate, are consolidated.

Knockout mutants, RNAi silencing, and overexpression of genes and, recently more frequently, genome editing tools such as the CRISPR–Cas system, represent powerful technologies, but they require similarly powerful protocols for functional characterization of the modifications made. Regular journals, many with high impact, specializing in the molecular biology of various organisms have strictly policed rules in many aspects of this work. However, where genes associated with SLM biosynthesis are concerned, often the creation, elimination, or change in titer of these products is assumed. Indeed, even the absolute function of genes targeted may not have been rigorously determined.

Onto this backdrop, bioinformatics is expected to deal with the vast expanse of rapidly growing data even, in the eyes of some, without recourse to rigorous "wet" science. Of course, we all welcome use of bioinformatics to provide shortcuts to the genes and regulatory systems of importance, but this tends to occur only where we have already accrued an extensive arsenal of knowledge. Few practicing scientists will disagree, but they are not those who are managing and funding science. In this, our defence of peer review is crucial, and yet the unbelievably naïve promotion of combinatorial chemistry went largely uncriticized until we could see the problems of the spectacular lack of diversity that the libraries represented, particularly compared with the diversity of naturally occurring SLM structures. Nevertheless, at the end of the bioinformatics exercise in making as much sense of next generation sequencing data as possible, comes the need for use of existing and only slowly growing knowledge of biosynthetic pathways gained from biochemistry and SLM studies on activities associated with ecological interactions together with functional studies in molecular biology.

To raise awareness of the value of Chemical Ecology, which has always been a highly interdisciplinary subject, and its overall methodologies, we must put our efforts unto the post-genomic context where molecular biologists are drowning in "big data". We can provide the crucial "phenotyping" and original experiments *via* bioassay-guided fractionation to find elusive genes that make and regulate production of the SLMs that are relevant and often crucial to biological interactions between organisms.

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