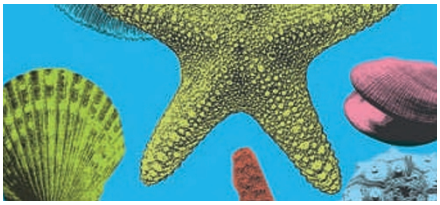
Drug discovery from natural products

Natural products have proved to be a rich source of therapeutic agents. Our two interviewees this month discuss natural-products research in academia and industry.



Frank E. Koehn, Ph.D.
Director of Biosynthetic and Discovery Analytical Chemistry, Wyeth Research, Pearl River, New York, USA.

At Wyeth Research, Frank Koehn leads a multidisciplinary research group that aims to advance drug discovery programmes by means of biosynthetic chemistry and the application of advanced analytical techniques. "My position involves coordinating the efforts of a diverse group of scientists — chemists, microbiologists, molecular biologists and experts in analytics such as nuclear magnetic resonance spectroscopy, mass spectrometry and bioanalytical chemistry. I also manage Wyeth's efforts with external alliance partners in these areas," says Koehn.

Since his Ph.D. in marine red tide toxins at the University of Wisconsin–Madison, USA, Koehn has been driven by a continuing interest in the biosynthetic capabilities of organisms (marine, plant or microbial) to make molecules that affect or manipulate other biological systems. "I am fascinated by the value of biologically active natural products in treating human diseases — uses that are seemingly unrelated to their native intent. But, as it turns out, the underlying biological effects and mechanisms of natural products are fundamental, and often go far beyond what scientists can design alone," he says.

Following postdoctoral work in bioactive plant natural products at the University of Pennsylvania, USA, Koehn noticed that a marine drug discovery programme, based at Harbor Branch Oceanographic Institution in Fort Pierce, Florida, USA, was seeking scientists. Koehn's application was successful and he remained there for 10 years, progressing to a senior investigator position. During this time, Koehn often worked with pharmaceutical companies to identify biologically active molecules. Although he found the work scientifically fascinating and intellectually gratifying, it was difficult to maintain a connection to the research projects once a compound reached later stages of development. Intrigued by the development of natural product-based drug candidates, Koehn applied to Lederle Laboratories, which subsequently became Wyeth Research. "I was attracted by potentially seeing a more direct impact of natural products in the lives of patients."

Now, 15 years later, Koehn hugely enjoys the collaborative nature of his work. "I find it most rewarding when our group is able to marshal together the necessary research skills to advance a drug discovery project, which, prior to that collaboration, did not seem possible. For example, it is now possible, particularly in the case of bacterial metabolites, to obtain molecules with structural alterations that cannot be achieved using synthetic chemistry by genetically engineering the producing organism. However, to do this productively requires the close collaboration of chemists, molecular biologists and microbiologists," he explains.

This requirement for collaboration to achieve drug discovery research goals has taught Koehn the importance of teamwork. "Teams that work together and collaborate well are often successful. Teams that do not are less successful. I have learned that effective collaboration can often overcome shortcomings in resources or even expertise because the teams that collaborate and communicate well are able to take advantage of and build on their positive results. Drug discovery and development is a vast enterprise, and it cannot be successfully done acting alone."

David J. Newman, D.Phil.
Chief, Natural Products Branch, National Cancer Institute, Frederick, Maryland, USA.

The Natural Products Branch (NPB) is part of the US National Cancer Institute's Developmental Therapeutics Program, which is the discovery and preclinical development component of the Division of Cancer Treatment and Diagnosis. "The NPB is one of two branches responsible for acquisition of chemical compounds for initial screening," says David Newman, Chief of the NPB. An example of a drug that has emerged from the NPB is the heat shock protein 90 inhibitor 17-allylaminogeldanamycin (tanespimycin; licensed to Kosan Biosciences — a wholly owned subsidiary of Bristol–Myers Squibb), which is currently in Phase III trials to treat multiple myeloma.

"We are also responsible for a worldwide collection programme searching for marine invertebrates, plants and microbes as sources of novel natural-product agents to be tested against cancer. These will subsequently be made available to entities worldwide (with the express permission of the source countries) for testing in screens related to any disease that is of interest to the National Institutes of Health," says Newman.

Newman's interest in the interplay between chemistry and biology began in the late 1950s through his first degree, which included 4 years of work experience as a chemistry technician and assistant analyst. In 1960, he qualified as a graduate chemist of the UK's Royal Institute of Chemistry by external examination. "One thing I have found is that a thorough background in chemistry makes learning biological systems a lot easier," says Newman.

During his postgraduate work at the University of Sussex, Newman's mentor, Professor John Postgate, Fellow of the Royal Society, first inspired Newman's interest in natural products. "John exposed me to the intricacies of metallo-proteins from a microbial-chemistry perspective and what these materials could do with earth, air, fire and water, rather than the methods required by chemists," he says. Since then, Newman's career has been directed towards "...using Mother Nature's secondary metabolites as leads to drugs in manifold pharmacological areas, irrespective of where they were first found."

Following postdoctoral work in the laboratory of Professor H. D. Peck Jr at the University of Georgia, USA, Newman's career path led to work in organizations such as SmithKline and French Laboratories, Philadelphia, USA; SeaPharm, Florida, USA; and Lederle Laboratories, New York, USA. He also held the position of Adjunct Professor at the Center of Marine Biotechnology, University of Maryland, USA. Throughout this time, one of the most important lessons Newman learnt was that networks of professional colleagues are the most valuable resource you can have, particularly when companies eliminate research areas.

Another lesson Newman values is advice he was offered back in the 1960s to think obliquely and approach problems in this way. Newman explains, "This can be best expressed as: look for the pointers from other scientific areas that might lead to an idea of how to tackle the challenges you have to deal with today."

WEBSITE
Career snapshots: http://www.nature.com/drugdisc/nj/nj_dd_arch.html