

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Marine Natural Products

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H&O What are marine natural products?

TM Marine natural products are chemical compounds made by marine organisms such as algae, marine sponges, ascidians, and molluscs, some of which have drug-like properties. Although it is not understood why, the hit rate—the percent of compounds or extracts that are scored as high positives in an assay for drug-like properties (eg, a specific enzyme inhibitor)—for these compounds is exceptionally high. Marine natural products also have great diversity in biologic activity and chemical structure, which is good for producing drugs.

Sponges and algae are favorable because they both have been around since the dawn of animals and have been useful in the study of organic chemistry for hundreds of years. Some people believe that these natural products are chemical defenses produced or retained by organisms to ward off potential predators. Some think they are chemical cues, whereas others assume they are antifouling organisms that suppress bacteria or viruses. In any case, it seems that marine natural products have adapted for specific roles, and we often find that the target for a drug is very similar to a target for a natural product. However, we can only speculate why that is.

H&O What is the mechanism of action for marine natural products with antitumor effects?

TM The mechanism varies. If you go looking for an antitumor drug—something that is cytostatic—you will find the most common mechanisms to be antitubulin or

antimitotic agents that interfere with microtubules and those that interfere with microfilaments. Having said that, other natural products have mechanisms of action that are very different. Trabectedin (Yondelis, Zeltia/J&J) is a new drug that entered the market in 2007; it is both a DNA alkylator and a disruptor of lesion repair mechanisms, affecting cell proliferation.

H&O How do we go about screening prospective products for biochemical potential?

TM We are somewhat constrained by the limits of our resources, so we start with a simple *in vitro* assay. For example, the assay may be based on growing human tumor cell lines for finding antitumor potential. We look for growth inhibition and cytotoxicity, which is the starting point for discovering a hit. Once we get a hit, we then advance to see whether it is a lead or a toxic compound; this process usually involves collaborative research with medical investigators, the National Cancer Institute, or other institutions. From there, the compound goes into a model where a xenograft is introduced, and tumor cells are implanted into nude mice. If the compound injected into the mice kills the tumor cells and the animal survives, we call that a success and progress to the next stage. Because this next phase of research is very expensive, academic-industrial collaboration is ideal. What we hope for is a committed industrial partner that understands natural products and recognizes that there are certain needs for these compounds. Natural products require time for development

and need a ‘champion’ that understands the hurdles of procurement, purification, and good manufacturing practice. Therefore, if there is hit activity that can turn into a lead, the natural product may do pretty well.

The history of developing marine natural products has been very successful in generating leads. I do not think it is possible to compare the history of the leads that have come out from combinatorial libraries across the world with the success rate of natural products. In their structures, natural products seem to have a built-in history of their adaptation by the organisms that produce them; it is almost as if they have been selected by nature over thousands of years.

H&O What are the challenges of applying marine-derived compounds to clinical trials, and what are the possible advantages?

TM Once a natural product has activity and a profile, and the compound looks promising, there is a massive hurdle which is seen with every marine natural product: how do you procure it?

The structures of these compounds are usually complex. For example, trabectedin was isolated 40 years ago from a sea squirt in the Florida Keys with interesting profiles that advanced it into animal trials. However, the unsettled question was: if trabectedin proved to be as successful as it seemed it would, how were we going to get enough of it to treat patients in a clinical trial—let alone enough to put it on the market? This question was answered when researchers found a way to make trabectedin from another complex natural product that could be fermented under conditions familiar in industrial biotechnology from the *Streptomyces* bacteria. Consequently, the trabectedin structure was built by utilizing this precursor, which was available in large amounts, and suddenly a method for manufacture was created. Presently, trabectedin is a drug that is marketed and synthesized in this way—a far cry from other hopeful alternatives which were tried, such as ‘aqua-farming’ the sea-squirt. However, the concern of procurement and scale up of marine natural products remains an issue and is one reason why industry has shied away from natural products.

I think the challenges associated with the application of natural products to clinical trials include the usual: compound properties, formulation, and bioavailability. However, there are other challenges as well, including the question of who has the rights to the compound if it comes from foreign waters or lands. If the compound is patented by an investigator but the investigator obtained it from a foreign land, there are issues associated with native title, indigenous rights, and whether benefits

should accrue back to the country of origin. These are legal matters, of which a number have been partially addressed by international conventions that are subscribed by some governments, including most of the developing countries around the Pacific rim. By and large, most investigators now recognize that if, for example, a compound is discovered in the waters of Papua New Guinea and is patented, part of that intellectual property belongs to the people of Papua New Guinea.

The history of the drug-like properties found in natural products tends to attest to their values as drug sources. A concern that often arises is whether a drug from a natural product is any better than one we can make in the lab. I think this is a difficult question because there are so many different factors that are involved. Yet, if one looks at the history and chemistry of natural products and how it is integrated in medicinal chemistry, approximately 40–50% of the drugs on the market are either derived from natural products or are natural products themselves. There is no doubt that there is a strong correlation between the molecular structures of natural products and those of the drugs we use. These include successful antitumor drugs like paclitaxel, which is a great success story.

The other and more specific issue is whether there is some scientific rationale for why natural products should be better than synthetic compounds. Again, the answer to this question is hard to pinpoint. There have been, nonetheless, studies showing that natural products more closely match the physical and chemical properties of drugs that are in the market. Mapping multivariate analyses have revealed that the structures of natural products look more like the drugs we use than combinatorial compounds, which have so far failed to produce significant drug leads.

H&O What has been the most exciting finding in marine natural products in regard to antitumor effects?

TM I think the most exciting contemporary finding so far has been trabectedin. Now, there are numerous marine drugs coming through the pipeline, some with very interesting drug profiles. We should see how that pans out in the next couple of years. No time in the past 25 years that I have been working in this area is as exciting as it is right now. It has taken a long time to get to where we are, and it has been a long struggle. It has taken a while for the appreciation of the science to catch up, but now we are at the point where drug companies are focusing routinely on natural products as leads for new compounds. The importance is not so much the natural products themselves, but the fact that companies see the natural

products as a template with which to build a better drug. The interesting thing is that larger pharmaceutical companies shied away from this research at the beginning, leaving it to become an investment and research opportunity for smaller companies.

The cutting edge with this research is whether we can take the genes that are responsible for making the enzymes that produce the natural product, remove them from their marine environment, and put them into a bacterium that is amenable to fermentation. This process is called heterologous expression. Once this technology is figured out, in principle, any promising natural product found in any niche in any part of the living world could be turned into a drug.

H&O Is there any ongoing research? What are some promising products?

TM There are ongoing trials in the United States, Europe, and the United Kingdom that are investigating trabectedin in different types of cancer. We reviewed

these studies in our article which was published this year.¹ Trabectedin has been in phase II trials for several tumors including prostate, breast, and pediatric soft tissue sarcomas. It is also being studied in combination with modified doxorubicin for relapsed patients with ovarian cancer. There are papers coming out on this topic almost monthly, indicating that this is a very active area of research. Right now, trabectedin is only approved for 1 type of cancer—soft tissue sarcoma, which includes liposarcomas.

It is interesting to note that trabectedin, 1 of the 2 marine natural products that are on the market, is a compound that is used in its unmodified form, meaning that there were no alterations made in synthesis to change the structure of the natural product. It turned out that, like paclitaxel, the natural product was the best candidate to market as a drug.

References

1. Molinski TF, Dalisay DS, Lievens SL, Saludes JP. Drug development from marine natural products. *Nature Rev Drug Discov*. 2009;8:69-85.