

## Arnold Demain



**A trailblazer in the field of antibiotics reflects on natural product discovery in the genomic age.**

Arnold Demain's storied career has spanned pioneering work on  $\beta$ -lactam antibiotics and fermentation microbiology at Merck (Whitehouse Station, NJ, USA), teaching and research at the Massachusetts Institute of Technology for over 30 years and being a founding scientific advisory board member of our predecessor, *Bio/technology*. In this edited interview, he discusses the prospects of new genomic technologies fueling a comeback for natural products as drugs.

**What areas of natural product discovery and biotech are we not paying attention to that we should be?**

**Arnold Demain:** I would say the discovery of new small-molecule natural products like the antibiotics. The emergence of resistant organisms is a developing crisis. I don't know what's going to happen here. But if governments aren't interested in doing this, I think it's going to be a disaster. I realize this is not a time to talk about the government spending more money, but I think we need something like a national institute—a new NIH [National Institutes of Health] institute on antibiotic and natural product discovery—because nobody has the money to do this.

**Why has natural product discovery hobbled behind other approaches to pharmaceutical discovery?**

**AD:** One reason is that once the low-hanging fruits were taken off the tree, companies kept discovering the same products. Then they invested a lot of money in failing technologies like combinatorial chemistry and things like that. And after companies got the cream of the crop, the industry felt it was too difficult. A second reason is that molecules, like antibiotics, don't fit the business models of pharmaceutical companies. With most of our antibiotics, you take them for a couple of days and you get well. So the usage is limited,

unlike a drug for a chronic condition that is taken every day for the rest of your life. But keep in mind that in recent years, natural products that are large molecules have become a new part of the pharmaceutical industry. I consider monoclonal antibodies to be natural products. They're booming and increasing every year. A lot of the natural product people that haven't been let go by the pharmaceutical industry are availing themselves of microbes to make larger molecules or applying microbial technology to the use of mammalian cells to make such products.

**Can you talk more about the scientific challenges associated with natural product discovery?**

**AD:** There are several technologies that have been around for a few years but that have not really been pursued in the major way that the pharmaceutical industry used to pursue something. For example, genome mining, i.e., genetically examining the organisms like *Streptomyces* for example, that make a lot of products. You look at the genomes and discover genes encoding groups of enzymes that allow you to predict that they are making natural products. Another one is metagenomics, since 99% of the bacteria have never been cultured in the lab. You take the DNA out of the soil and you put them in *E. coli*, and you now find out what these environmental microbes make. There's only one little company, NovoBiotic Pharmaceuticals (Cambridge, MA, USA), that is learning how to culture these microbes and finding new products being made. There's so much technology out there that is not being exploited in a major way.

**Where in this area can genomic technologies be best applied?**

**AD:** The marine environment is one story I am very familiar with. The ocean is great, because there are all sorts of interesting organisms including *Streptomyces* that no one thought existed in the ocean, but they certainly do. Bill Fenical's group at the Scripps Institution of Oceanography (La Jolla, CA, USA) has been discovering compounds for years. I was on the board of a company which he started called Nereus Pharmaceuticals (San Diego). The first two compounds that were given to Nereus by Fenical's group are in clinical trials now for cancer.

**To what extent is technology rather than business issues, such as an excessive focus on blockbusters like statins, the problem?**

**AD:** It's interesting you mention statins, rather than some synthetic compound, because statins are microbial products. They inhibit the key enzyme in cholesterol synthesis. [Akira] Endo in Japan and Merck worked on the enzyme and came up with natural products that inhibited it. There are many enzymes in medicine that have to be inhibited, and the story of statins provides an example of how one could go after them. So I say there are current problems that are solvable by the [natural product] technology. But we need the dollars.

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**With R&D funding increasing in China and India, which have their own tradition in herbal medicines, are natural products likely to be a larger part of the drug pipeline going forward?**

**AD:** No, I don't think so. India and China, of course, are busy in the pharmaceutical area. But as far as I know, they are not investing in discovery of molecules, even though they're the ones who discovered these herbal medicines and there must be active compounds in there. And that's a pity, because there's no doubt that these herbal medicines work. But they're just not investing or discovering molecules. They keep working on these same molecules that we in the West discovered years ago. They have a real opportunity, because our pharmaceutical industry has dropped out. Europe's pharmaceutical industry has dropped out. But if somebody doesn't put a batch of money in there, nobody is going to isolate those compounds. **15**