The directed mutagenesis of GFP described above is not the first successful effort to produce useful GFP mutants. Previous efforts have used random mutation of GFP followed by the isolation of those mutants with desirable fluorescence properties. Aurora Biosciences, for example, already has mutants of GFP that emit ultrabright green, as well as yellow and two shades of blue fluorescence. They believe these mutants of GFP will be critical components for the development of ultra-high-throughput screening assays [*Drug Discovery Today* (1996) 1, 313–314]. The availability of the molecular structure of GFP will now provide a sound chemical understanding of the altered fluorescence properties of the mutant GFPs that have already been produced by random mutagenesis. Moreover, it will provide a rational approach to produce directed mutants that may never have been explored without the insight provided by the newly derived molecular structure.

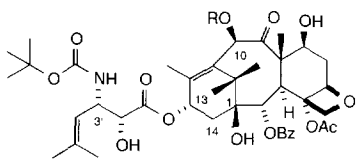
GFP is already proving to be a highly useful agent for exploring cell structure and for assay development. GFPs emitting different colors can be used as reporters to monitor the activation of multiple genes, and also as protein tags. The glowing protein can be attached to other proteins on either its amino or carboxyl terminus and used to monitor their transit or to follow biochemical reactions and interactions in living cells. GFP can be readily expressed in a variety of different cells including yeast, *Drosophila*, zebrafish, mammalian, plant, bacteria and slime mold cells. It can be directed to specific areas of the cell by fusion to targeting sequences, and it has utility as a tracer to determine the lineage of a particular cell. Once expressed, the protein is very stable and is resistant to degradation by proteases. In drug discovery it will undoubtedly be very useful in conjunction with imaging technologies for the development of ultra-high-throughput screening assays.

In nature, GFP dramatically illuminates marine coelenterates, such as the jellyfish *Aequorea victoria* found in the waters off the Pacific Northwest of the USA. It works in conjunction with aequorin, a Ca^{2+}-sensitive, luminescent protein that has also proved to be a highly useful tool for cell biologists in measuring the concentration of intracellular Ca^{2+}. In the jellyfish, GFP absorbs the blue chemiluminescence of aequorin and acts as a transducer by emitting it as green fluorescent light. Many of the marine invertebrates have evolved light-producing systems, but few of the molecular components of these systems have been isolated, cloned and made available for use in biotechnology. Perhaps the obvious utility of GFP will spur additional activity in this area.

Robert W. Wallace

Taxol moves on

Small and easy-to-carry-out changes in the basic structure of the drugs taxol and taxitere increase their potency against various types of cancer cells in the test tube, according to US researchers. The discovery could lead to a second generation of these powerful anticancer compounds that may also show less side effects than the present formulations.



One of the taxol derivatives with increased antitumour activity.

Dr Iwao Ojima (State University of New York, Stony Brook, NY, USA) described at a lecture at the University of Cambridge in October how he and his team have discovered that modifying the amino acid side chain at the C-13 position as well as the C-10 acyl group of the basic taxol structure (see Figure) boosts the drug's cytotoxic activity against ovarian, non-small-cell lung, colon and breast cancer cells.

He and his team set out to build a taxol derivative that would overcome taxol's side effects and multi-drug resistance, which has recently been reported in clinical trials. In early experiments they noticed that certain of their C-3′ substituted taxoids were more potent against a particular drug-resistant cancer cell line if the free hydroxyl (OH) group at the C-10 position was substituted with an acetyl group. They decided that this might provide a clue to building a second generation taxoid and began synthesizing various analogues with alkyl and alkenyl groups at the C-3′ position as well as different acyl groups at C-10.

According to Ojima, all but one of their new taxoid compounds were more effective than taxol (paclitaxel) or taxotere (docetaxel). He adds that changing the C-13 side chain as well as the C-10 acyl group quite significantly still leads to effectiveness against standard cancers.

Three of the taxoids were found to be more potent than either taxol or taxotere against drug-resistant breast and ovarian cancer cell types by two orders of magnitude. Ojima points out that the breast cancer type has 180-fold resistance to the drug doxirubicin and so alternatives are keenly sought.

The team has already found that one of their taxoids, dubbed SB-T-1213, shows strong antitumour activity in nude mice against melanoma, and the other compounds are currently being investigated in detail to uncover the relationship between structure and activity.

The team also described the synthesis and assaying of their taxoids in the *Journal of Medicinal Chemistry* (1996) 39, 3889.

David Bradley

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