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Solving the "Taxol dilemma"

Obtaining enough of the anticancer agent paclitaxel (Bristol-Myers Squibb's Taxol) from its natural sources—one of which, the Pacific or Western yew, *Taxus brevifolia*, is listed among the world's endangered conifer species—remains a vexing problem. The need for new solutions grows as the demand for taxane drugs continues to increase; currently, paclitaxel and its semisynthetic analog docetaxel (Rhône Poulenc Rorer's Taxotere) are approved for the treatment of breast and ovarian cancer, and many clinical trials are underway for a number of other indications, including lung cancer, Kaposi's sarcoma, and lymphoma.

The original solution—cutting down and stripping tens of thousands of trees to harvest an astonishingly small (13,500 kg of *Taxus brevifolia* bark yields about 1 kg of paclitaxel) amount of active drug—set off an environmental firestorm, and the unhappy circumstances pitted environmentalists interested in preserving and maintaining these plant resources against angry cancer patients and researchers. Alternative production methods—total chemical synthesis of paclitaxel (which requires upward of 30 steps), biosynthesis by a yew tree fungus, *Taxomyces andreanae*, and *Taxus* plant cell culture—have moved the field forward, but none has solved the problem of how to collect and/or manufacture enough of the compound(s).

Thus far, the highest productivity—153 mg paclitaxel/L in 6 weeks—of plant cell culture has not been sufficient to be economically feasible. But in this issue (pp. 1129–1132), Yukihito Yukimune and collaborators from the Bioscience Laboratory at Mitsui Petrochemical Industries in Japan describe an approach that may bring paclitaxel plant cell culture closer to being a commercial option. By exposing cell suspension cultures to the cell signal transducer methyl jasmonate, Yukimune et al. obtain paclitaxel yields exceeding those of previous culture efforts by a factor of 6 (300 mg/L in 2 weeks). They have also partly addressed the problems associated with scaleup—to a level of 200 liters. This is a good beginning—nowhere near the 100,000 liter production requirements of industry, as John Pezzuto points out in his commentary on this research—but one that is worth economic evaluation.

Much effort is being devoted to bringing paclitaxel production up to the mark: There are other groups working on manipulating culture growth conditions to achieve higher yields; some are attempting semichemical synthesis; some are trying to extract more paclitaxel from less bark; others are looking at commercial cultivation of faster-growing, more potent yews. Soon to be published, the description of *Pestalotiopsis microspora*, a fungus isolated from yew that produces paclitaxel yields of 50 mg/L, represents another step forward. And on the genetics front, the gene complex responsible for paclitaxel ring synthesis in *Taxomyces andreanae* has recently been isolated by Cytoclonal Pharmaceutics of Texas.

According to the US National Cancer Institute (Bethesda, MD), 45% of anticancer drugs approved for commercial use are either natural products or are derived from natural products. Thus, the lessons learned from solving the paclitaxel scaleup dilemma—maintaining a natural resource while developing sufficient product to go into the clinic—will stand biotechnology in good stead as it continues to turn to plant and marine compounds for leads in the pursuit of new therapeutics.

Nomenclature on the fly

Investors may have been somewhat prickled by the announcement in mid-July that two Cambridge, MA biotechnology companies, Biogen and Ontogeny, were to embark on an collaboration worth up to $80 million for the commercialization of three "hedgehog" cell differentiation proteins. Their faith in the sanity of biotechnologists could not have been helped by learning that the three proteins are known as "Desert," "Indian," and "Sonic" hedgehog. But they should expect worse as functional studies using the fruit fly, *Drosophila melanogaster*, get underway in earnest at genomics companies (see "Sequana worms ahead of the pack," p. 1073).

Gene discovery in *Drosophila* has often followed phenotype observation. Thus, "hedgehog" flies are developmental mutants, the embryos of which are covered with spine-like structures (denticles). Humans and other vertebrates often have several genes homologous to a single *Drosophila* gene; hence the "Desert," "Indian," and "Sonic" variants of "hedgehog," epithets that are meaningless in and of themselves but which serve both to differentiate the homologs and to underline their lineage.

For nearly a century since Morgan, the *Drosophila* genetics community has enjoyed boundless freedom in the naming of genetic variants. Whereas yeast or *Caenorhabditis elegans* geneticists have been constrained to curt acronyms by nomenclature conventions allowing only three letters followed a number, Drosophilists have gloried in genetic variants such as *Don Giovanni*, *bang-senseless*, and *Killer of prune*.

Some of the *Drosophila* canon has been borne of necessity. Thus, just as those living within the Arctic Circle have 17 different words for snow, so native *Drosophila*-speakers need to distinguish many degrees of reduced stature. Flies can be *small*, *tiny*, *diminutive*, *miniature*, or—most perfunctorily—*undersized*; there are Tolkienesque variants—*wizened*, *dwarf*, and *elfin*; and the politically incorrect *squat*, *puny*, and *runt*.

The *Drosophila* community has then overlaid upon these phenotypes both its fertile collective imagination and its striving for individual identity or notoriety. Thus, *windbeutel* conveys both the morphology of the embryonic variant (puff pastry containing whipped cream) and the origin of its discoverers (Germany). By the same token, the discover of *stranded-at-second* must surely have been a baseball fan; of *pratfall*, a slapstick comedy aficionado.

The rise of reverse genetics and the dash for genomics may soon preclude *Drosophila* researchers from waiting, as most do now, to discern function before naming genetic loci. Will that matter? Probably not. Most *Drosophila* locus names never convey precisely the role of a given gene or protein. They certainly do not suit the rigors of a systematized (computerized) genetics. Yet they have one supremely important quality: Like good advertising slogans, they are memorable. *Four-wheel drive*, *prawny abdomen*, and *twisted genitalia* evoke strong images, providing hooks upon which information processors of a merely human kind can readily hang bits of related data. And in linking up the multidimensional genomic puzzle, memorability may prove to be an important quality indeed.