DRUG DESIGN

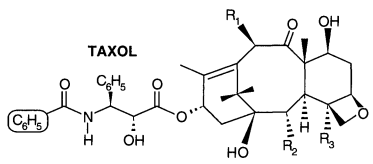
Chemists Vie to Make a Better Taxol

SAN FRANCISCO—Ever since last summer, when clinical trials with human patients indicated that taxol may be remarkably effective against advanced breast cancer, this minor constituent of the bark of yew trees has become a celebrity molecule. Like most celebrities, it has serious failings: toxicity, poor solubility in water, and, worst of all, scarcity. But chemists are working hard to turn the drug into a true hero.

At the American Chemical Society (ACS) meeting held here last week, researcher after researcher came forward with schemes for boosting the taxol supply and improving on the molecule itself. Some hope to modify other natural taxol-like molecules; others are aiming for a complete chemical synthesis of the drug. On the way, they are spinning out as many variants of the basic molecule as they can, in the hope of finding new taxol-like compounds that could be more potent, less toxic, and easier to formulate than the original. In the end, remarked Stanford University taxol researcher Paul Wender, "taxol is not the drug we want to use [routinely]."

Currently, the only source of taxol allowed by the Food and Drug Administration (FDA) for clinical use is the bark of the Pacific yew tree, which grows in the same Northwest forests protected to safeguard the spotted owl. Stripping the bark kills the tree, and with 100,000 potential recipients of the drug annually in the United States alone, each requiring the taxol of six trees, the Pacific yew could quickly become scarcer than the spotted owl (*Science*, 28 June 1991, p. 1780). That raises conservation issues, but—more to the point—it means that this taxol reservoir would quickly run out if the drug became standard therapy for the breast, ovarian, lung, and other cancers against which it has shown promise. "We need alternative sources," says pharmaceutical chemist Matthew Suffness of the National Cancer Institute in Bethesda.

Fortunately, the high stakes, coupled with the laboratory challenge of the molecule itself—a complex multi-ring molecular core adorned with chemical side chains—are attracting scores of medical and organic chemists. Registering the boldest claim at the meeting was Pierre Potier of the Chemical Institute of Natural Substances in Gif sur Yvette, France. He and his colleagues, Potier argued, have bypassed taxol's main drawbacks in one fell swoop—by bypassing taxol itself. In its place they use a chemical precursor known generally as baccatin III, found in the leaves of the European yew. In a few chemical steps they convert the precursor into a now-patented chemical analog of taxol called taxotere. At a press conference, Potier touted taxotere as more environment-friendly than taxol—because the leaves grow back after being harvested—and easier to administer because it is more soluble in water. He also noted that taxotere was moderately more effective than taxol in early clinical trials against some types of cancers. "Taxotere looks like the drug to be used in the next few years," Potier enthused.



Perhaps, other taxol researchers concede, but taxotere will face competition from other taxol variants in earlier phases of development. Organic chemist Robert Holton of Florida State University, for example, has found a way of synthesizing chemical appendages and linking them to naturally derived molecular cores such as baccatin. He and co-workers already have more than 60 taxol analogs stockpiled.

These strategies for altering natural taxol-like molecules still rely on extracting tiny amounts of ingredients from large masses of plant tissue. Wender of Stanford is trying to make taxol from something much simpler and more abundant: a constituent of pine trees called pinene. (As cheap as dirt—well, potting soil to be exact, says Wender.) The trick is to convert pinene into the complex tricyclic core of taxol in a mere five chemical steps, a process relying on expertise in synthesizing eight-carbon rings, developed largely by graduate student Tom Mucciaro in the 1980s. In another handful of steps, the researchers can adorn two of the core's rings with the same chemical groups found on the genuine item.

The next hurdle, Wender says, is to do the same for the third ring. That would put his group in spitting distance of a total laboratory synthesis of taxol, because Holton already has shown the way to linking the core to the other large taxol component—a 33-atom appendage. Wender hinted at a press conference that his team may be on the brink of succeeding. If so, the group may become the first to open a major inexpensive route to taxol and variants—though any synthetic or semisynthetic taxol would face a new FDA approval process.

Just to remind ACS attendees that chemistry may not have all the answers where taxol is concerned, Arthur Goldstein of ESCA genetics Corp. in San Carlos, California, described a biological approach to the supply problem. His is one of several companies growing the taxol-producing cells of the yew in cell culture. Goldstein expects that his company will be making kilogram quantities of this tissue-culture taxol by next year.

All this activity is bringing researchers closer to what Wender calls the key reward: "to give patients who need taxol, taxol."

–Ivan Amato

ASTROPHYSICS

Quasars: Ablaze With Gamma Rays

Nothing shines quite like quasars—mysterious, distant objects giving off astonishingly intense emissions of light, radio waves, and x-rays. And astronomers now know they hadn't seen the half of it. The orbiting Gamma Ray Observatory (GRO) has now found 11 quasars that give out most of their power in gamma rays—a kind of radiation missed by previous observations. When the gamma rays are added to the known emissions, they boost each quasar's total energy output to the equivalent of 100 trillion suns, says GRO project scientist Neil Gehrels. That puts these "gamma ray quasars" in the running for the title of most luminous known objects in the cosmos.

The finding has posed a whole series of new quasar puzzles. For one, "Nobody thought a major fraction of the energy of quasars would come from gamma rays," says astrophysicist Richard Mushotzky of NASA's Goddard Institute for Space Studies. "The models we had didn't produce gamma rays," he adds, "which means [the models] are wrong."

What's more, the GRO spotted gamma rays coming from only some, not all, of its quasar sample. A clue to that mystery came when astronomers realized that three of the gamma-ray sources belong to a subset of quasars called BL Lacertae objects. These astrophysical exotica give off polarized light and have other features suggesting that their radiation escapes in a directed beam, like that of a flashlight. Astronomers are guessing that the same could be true of the gamma rays from many quasars—or even all of them. In that case, says Gehrels, what we see depends on which way the beam is pointed: The gamma ray quasars just detected would be the ones pointed right at Earth.

But if that's true, it only raises yet another puzzle: What mechanism could concentrate the quasar's energy into beams? For now, scientists have a good idea only of the energy's ultimate source: matter heated by friction as it is gobbled up by a massive black hole. But as for the details of the energy generation, they can only agree with National Optical Astronomy Observatories researcher Todd Lauer: "Black holes are messy eaters."

–Faye Flam