

teams in Japan, Spain, and the United States have come up with the same result, Song adds.

By itself, that finding doesn't prove that excess *DYRK* causes Down's problems; the critical chromosome 21 region contains about 50 genes in all. But the Song team also found that in mouse embryos, the *DYRK* gene is expressed in the same places—areas such as the gray matter of the brain, the spinal cord, and the retina—that are defective in Down syndrome.

Instead of doing a genetic search for key Down syndrome genes, Rubin and colleague Desmond Smith at the Lawrence Berkeley lab homed in on *DYRK* by looking at the behavior of several new strains of mice, each carrying a part of the crucial human chromo-

some 21 region. One strain, which did poorly in simple learning tests, contained a stretch of human DNA 180 kilobases long that includes *DYRK*. Smith and his colleagues reported in late October at the American Society of Human Genetics meeting in San Francisco. "It's like a pincer movement," he says. "We both landed on the same gene."

The two prongs of the pincer show that any departure from the gene's normal activity level can be dangerous. The mice's problems, like those of Down's patients, were caused by an extra copy of the *DYRK* gene, while the mutant fruit fly's were caused by having too little of *minibrain*'s protein product. "You need exactly two copies of the gene," Smith concludes. He cautions, though, that more work is

needed to confirm that *DYRK* is the gene at fault in the 180-kilobase region.

Assuming that it is, it's unlikely to work alone. Using mouse genetic engineering studies similar to those of Rubin and Smith, a French team, led by Dahmane Nadia of the Hospital Necker in Paris, has found that another chromosome 21 gene, which lies outside the 180-kilobase region and is the human equivalent of the fruit-fly *single-minded* gene, seems to lead to learning problems in mice with an extra copy. Sorting out how these two genes, and possibly others, contribute to Down's and to normal neural development, says Smith, is going to make "for a very exciting next few months."

—Elizabeth Pennisi

## CHEMICAL SYNTHESIS

### Tumor-Killer Made; How Does It Work?

The promising anticancer properties of taxol and its relatives have a way of sparking hot competitions. In 1994, two groups tied in the race to complete the first total synthesis of taxol, a name trademarked by Bristol-Myers Squibb (*Science*, 18 February 1994, p. 911). Now, in a contest to synthesize a related compound, two groups have again crossed the finish line in a virtual dead heat. In this sprint, the groups, one led by Samuel Danishefsky at the Memorial Sloan-Kettering Cancer Center in New York, the other by K. C. Nicolaou of the Scripps Research Institute in La Jolla, California, synthesized a bacterial compound known as Epothilone A, which kills cultured tumor cells in a manner similar to taxol, thwarting their ability to divide.

Although the structure of Epothilone A is less complicated than that of taxol, its synthesis represents "a great achievement," says Gerhard Höfle, an organic chemist at the National Biotechnology Research Institute (Gesellschaft für Biotechnologische Forschung) in Braunschweig, Germany. The ability to build these molecules from scratch will let chemists alter their structures and possibly improve their properties, says Höfle. "No drug is so good that you can't improve upon it," he says. Analogs of the compound could also help researchers conclude yet another race, which is still under way: a competition to understand these compounds' exact *modus operandi*.

To synthesize the molecule, both groups started with commercially available materials and then used about 20 synthetic steps to build these compounds up into separate fragments, which they then linked together to form the compound's double-ring-shaped structure. The specific fragments and the chemistry by which the two groups linked them differed, however. Danishefsky and his colleagues report their findings in the De-

cember issue of *Angewandte Chemie, International Edition in English*. Nicolaou and his colleagues, who synthesized the molecule using two different schemes, will publish their results in two separate issues of the same journal early next year.

Epothilone, which was discovered just last year by researchers at Merck to kill cells like taxol, is not alone in that ability. Researchers are also tinkering with another compound known as discodermolide, which was synthesized in 1995 and shown earlier this year to kill cells in much the same way. Epothilone may have some advantages over the competition, however. Unlike taxol and its close relatives, epothilone is water-soluble, which could make it easier to administer to patients. And unlike both taxol and discodermolide, it can be produced cheaply in large quantities by bacterial fermentation.

All three molecules appear to have one critical feature in common: the ability to prevent cells from reproducing by paralyzing the microtubules that ordinarily pull chromosomes to opposite poles of a dividing cell. Now, researchers hope to learn just how they do so. Past work with taxol and its analogs has shown that three regions of the molecule—known as a C-13 side chain, a C-2 benzoate, and a hydroxyoxetane ring—are all critical to the molecules' activity, says Jeffrey Winkler, an organic chemist at the University of Pennsylvania, Philadelphia. Although epothilone contains atomic building blocks similar to those that make up these critical regions, x-ray

images of the two molecules indicate that "the structures are very different," says Danishefsky.

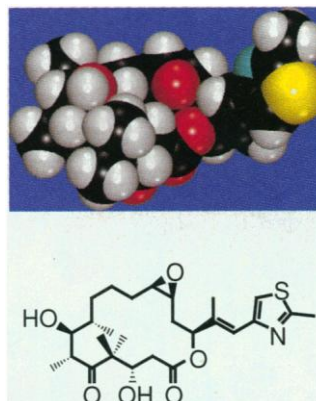
To see how the two different structures could have similar biological effects, Winkler and his Penn colleague Paul Axelsen compared computer models of taxol and epothilone. In an upcoming report in *Bioorganic and Medicinal Chemistry Letters*, the researchers report that the molecules could change their shapes and adopt similar stable conformations in which 13 of the 15 atoms in the large ring in epothilone line up with corresponding atoms on taxol, including the C-13 and C-2 groups. This match, says Winkler, suggests that these conformations are the ones responsible for the molecules' biological activity.

If so, Winkler and Axelsen believe that the C-13 and C-2 groups may fold together to represent one recognition site that taxol

uses to bind to its target on microtubules, and that the hydroxyoxetane ring either represents an independent site or a structural beam that holds the C-13 and C-2 groups in place so they can do their job. Next, the researchers hope to look at models of discodermolide to see if one of its conformations fits with this model as well.

Höfle notes that other teams, including his own, are now testing these ideas in the laboratory by analyzing how epothilone, discodermolide, and their analogs bind to the protein target on the microtubules. In the end, researchers hope, all these many races will lead to a single kind of prize: a way to design new compounds that will make more potent and safer anticancer drugs.

—Robert F. Service



**Model killer.** The synthesis of Epothilone A, which kills like taxol, may help make it even more potent.

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