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New pain relievers are moving through research labs. NICOLAS BAZAN hopes his drug may ease future aches. BY ALIYA STERNSTEIN

SIR JOHN VANE KNOWS A LOT ABOUT PAIN. THE BRITISH pharmacologist won the Nobel Prize in Medicine in 1982 for discovering the link between aspirin and pain signals in the brain. Now he says scientists can do a better job at pinpointing and relieving pain.

The prognosis: Researchers are busily developing a new generation of drugs for everything from minor pangs to postsurgical trauma, without the side effects that have dogged some of the more recent entrants in the pain relief market. If all goes well, the first of these new drugs should be available by prescription by 2005 and over the counter within ten years.

The $14-billion-a-year prescription pain drug industry has seen some torrid growth lately, thanks to the new class of so-called COX-2 inhibitors targeted at arthritis and pain. Sales of Pharmacia’s Celebrex should pass $2.9 billion this year, up from $2.2 billion in 2000. Merck’s rival drug, Vioxx, should generate $2.1 billion this year, up from $1.5 billion in 2000. Meanwhile sales have flattened for name brand over-the-counter drugs such as Tylenol, Aleve and Nuprin, which accounted for $2.5 billion of the $3 billion segment, according to Mark Goldstone, who tracks industry data for marketing conglomerate Euro RSCG.

But a recent string of woes have put a hurt on the pain relief business. In June Express Scripts, one of the biggest managers of pharmacy benefits in the U.S., told its clients that Celebrex and
Vioxx provide only a narrow benefit over ibuprofen (the branded version is Advil) and naproxen (Aleve), which, as generics, are vastly cheaper (see box). Complaints have dogged Celebrex and Vioxx since their introduction in 1999. Accusations include increased risk of gastrointestinal bleeding and heart attacks, as well as slowdowns in the ulcer-healing process.

While aspirin, acetaminophen (Tylenol) and most over-the-counter pain relievers are considered very safe and effective, some troubles have recently emerged for them, too. In September a Food & Drug Administration advisory committee met to review data on the 458 acetaminophen-overdose-related deaths every year in the U.S., of which 100 are unintentional. As a result, the FDA is considering changing acetaminophen warning labels to identify the risk of liver toxicity. Another possible label change would warn that excessive doses of ibuprofen and naproxen may increase your risk of gastrointestinal bleeding and magnify kidney damage for those with pre-existing conditions.

The physiology of pain relief is still only partly understood, even though aspirin has been around since 1899 and Johnson & Johnson’s McNeil Laboratories started selling TYLENOL in 1955. John Vane won his Nobel by discovering in 1971 that aspirin and similar drugs inhibit an enzyme which makes prostaglandins, compounds released in response to inflammation. This prostaglandin-producing enzyme is called cyclo-oxygenase, or COX. Vane’s research led drug companies to target pain by stopping the COX enzyme from producing prostaglandins.

As it turned out, aspirin and its cousins ibuprofen and naproxen were quite effective in shutting down both COX-1, which is active in the stomach and in blood-clotting platelets, and COX-2, which exists primarily at the site of inflammation and in the brain. The idea behind COX-2 inhibitors, such as Celebrex and Vioxx, was to spare the stomach lining by targeting only COX-2.

Left out in this research was acetaminophen, a brain drug that works on neither COX-1 nor COX-2. Scientists had no hard evidence on how it works, but the recent discovery of the COX-3 enzyme by Brigham Young University scientist Daniel Simmons could possibly hasten the arrival of the next Tylenol.

At the forefront of this work is fledgling firm St. Charles Pharmaceuticals in New Orleans. Its founder, Nicolas Bazar, a 60-year-old neuroscientist, has a seemingly simple and elegant answer to the pain problem: Chemically combine a derivative of acetaminophen with a salicylinate (aspirin) component. Adding a sweet substance solves the problem of liver and kidney toxicity, allowing him to deliver safely a far more potent dose of relief that he suspects may target the COX-3 enzyme.

St. Charles, named after the trolley-tracked avenue near Bazar’s home, is in very early stage clinical trials with its new drug, SCP-1. “There’s nothing out there that is as effective, that is non-narcotic … and is at least as powerful as acetaminophen,” Bazar claims, adding that unlike acetaminophen, his drug will not lower fever.

Ten years ago the Argentinean-born Bazar joined up with Julio Alvarez-Builla, an organic chemist at the University of Alcala in Spain, to develop better painkillers that had fewer side effects. It turns out that, in excess quantities, acetaminophen’s breakdown products latch on to the FAS ligand of liver cells. That protein is a switch that tells a cell to self-destruct. The addition of a saccharinlike component prevents this FAS-triggering. In mice, 27 milligrams of acetaminophen killed half of the subjects, whereas twice as much SCP-1 was harmless.

Now humans are the guinea pigs; 40 are consuming up to 900mg of SCP-1 a day. If SCP-1 gets through the FDA’s hoops, the new morning-after-Mardi-Gras pain relief could be available by prescription in 2005 and without perhaps by 2007.

Bazar wants to line up a big drug firm to peddle the potion. It won’t be J&J’s McNeil Consumer & Specialty Pharmaceuticals division, which had not heard of his company when a FORBES reporter called. J&J is not saying much about its research into acetaminophen improvements, except that it wants to ascertain whether or not COX-3 exists.

Other firms have new pain relief drugs in the pipeline. AstraZeneca has doped its version of a COX-2 inhibitor with nitrous oxide—yes, laughing gas—to soften the gastrointestinal blow. Nitrous oxide increases blood flow to the stomach, thickening the mucous lining that COX-2’s tend to wear thin. In early-stage human trials in May 2000, scientists observed 66% fewer stomach erosions in 31 patients treated with a nitrous oxide version of a COX-2 inhibitor, versus naproxen. This drug could conceivably be ready by 2006.

Novartis also has a new anti-inflammatory, Prexige, for acute and chronic pain. Due out in 2004, it could work faster, longer and cause fewer ulcers than other COX-2s.

And Pharmacia’s new injectable COX-2, called Dynastat, could supplement (or supersede) morphine. Approved in Europe, Dynastat eases suffering for postsurgical and office patients in minutes, instead of the up to an hour it takes COX-2 pills to kick in. The drug, still undergoing clinical trials in the U.S., seems to have the same side effects as the other COX-2s, but in tests against morphine, ketorolac (Toradol) and placebo, Dynastat was superior to morphine and placebo, and comparable to ketorolac in potency and duration.