Two in one

Norvasc and Lipitor are both blockbuster drugs made by Pfizer, one for high blood pressure and the other for high cholesterol, respectively. They now have something else in common—namely, a home in each pill of Caduet, one of Pfizer's newest products approved by the FDA.

Caduet—a combination of amlodipine besylate and atorvastatin calcium, the active ingredients of Norvasc and Lipitor—is being billed as "the first medicine to treat two different conditions in one pill."

"By treating both conditions at the same time, physicians can help patients reduce their risk of developing cardiovascular disease," says Joe Feczko, Pfizer president of worldwide development.

In clinical trials of 1600 subjects, about 57% reached both the blood pressure and cholesterol targets for their age. Pfizer points out that the same treatment goals are met by only 10% of the 30 million Americans with both of these conditions.

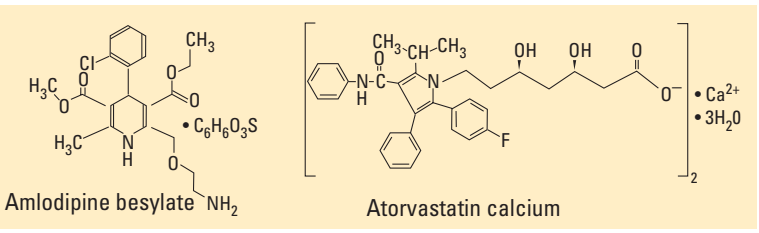
Caduet's impact on preventing heart disease remains to be seen. However, the drug's entrance into the market will certainly give Pfizer more economic mileage from its blockbusters. Although patents on Norvasc are to expire in 2007, the new combination product will have patent protection until 2018.

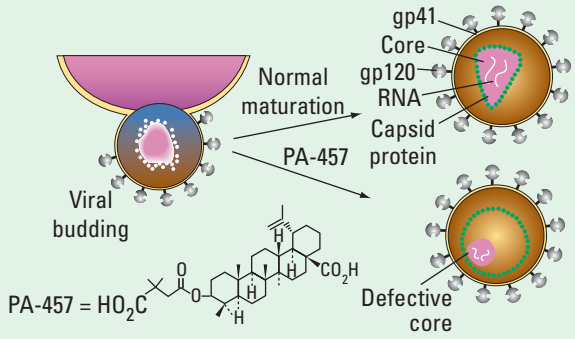
Eli Lilly recently made a similar move with Symbyax, which entered the U.S. market in January. The drug pairs Zyprexa and Prozac—the latter of which lost its patent protection several years ago. Lilly is promoting the drug as the first medicine to treat depression associated with bipolar disease.

Another drug that may soon emerge on the U.S. market (it was recently approved in Mexico) brings together not only two medicines but also two companies. Merck and Schering-Plough have submitted a New Drug Application for Vytorin, which contains Zocor, Merck's high-selling cholesterol-lowering statin that faces likely generic competition in 2006, and the newer intestinal cholesterol absorption inhibitor Zetia, developed by Schering-Plough and co-marketed with Merck. Zetia has been shown to substantially augment statins' cholesterol-lowering activity.

Combination drugs are not a completely new concept. But according to a recent report from Cutting Edge Information, $80 billion in blockbuster medicines will face patent expiration and generic competition by 2007. Seeking opportune drug pairings may be a new weapon in the arsenal to combat this threat.

—DAVID FILMORE





Late-stage inhibition. PA-457 blocks viral maturation, resulting in an HIV core structure that is noninfectious. (Copyright 2004 Panacos Pharmaceuticals.)

HIV drug trials

The FDA has given the okay for clinical trials to begin on the first of a new class of HIV drug candidates called maturation inhibitors. Panacos Pharmaceuticals will initiate Phase I studies focusing on the safety and pharmacokinetics of an orally available drug, PA-457, in uninfected volunteers. The drug was discovered in collaboration with Professor of Pharmacy K. H. Lee at the University of North Carolina at Chapel Hill.

"PA-457, as the first HIV maturation inhibitor, offers a completely novel approach for treating HIV/AIDS", says David E. Martin, vice president for drug development at Panacos.

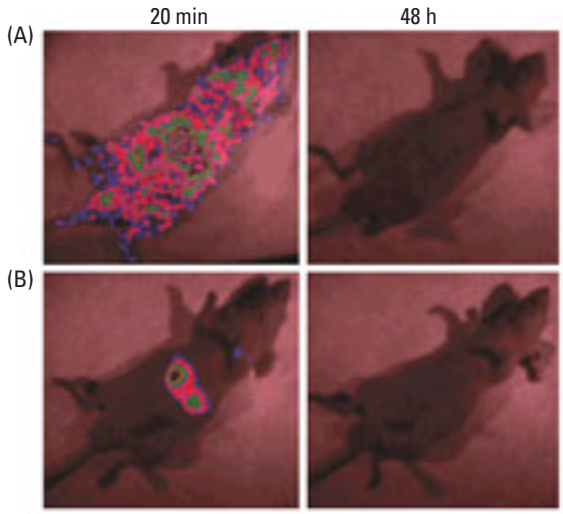
Maturation, which occurs when new virus particles are released from infected cells, is a key step in viral replication. PA-457, or 3-O-(3′,3′-dimethylsuccinyl)betulinic acid, disrupts the late-stage viral maturation processes of HIV's Gag protein. The Gag protein forms the capsid shell around a retrovirus's RNA and establishes a viral core structure. Treatment with PA-457 causes this core structure to be defective and noninfectious.

In recent years, drug resistance has become a dramatically growing problem in the treatment of HIV. PA-457 has shown potent activity against HIV strains resistant to approved drugs because it targets a different point in the virus life cycle.

Preclinical studies have confirmed an absence of cross-resistance between PA-457 and other classes of HIV drugs. And other results show the drug works in synergy with approved HIV drugs to block HIV replication and has a low probability for significant interactions with other antiretrovirals.

Panacos is looking to proceed quickly with clinical development. "If the data are supportive, we will rapidly move on to test PA-457's antiviral potency in HIV-infected individuals later this year," Martin says.

—KIMBERLY S. CLEAVES



Glowing success. Using a low-light imaging system, researchers could follow the real-time distribution and elimination of light-emitting *S. typhimurium* (A) and *V. cholerae* (B) in nude mice. (Adapted with permission from Yu, Y. A.; et al. *Nat. Biotechnol.* **2004,** *22,* 313–320.)

Light-emitting microbes

That bacteria and viruses exist in human tumors has been known for several decades, but how they get there and avoid the host immune system are poorly understood. Biochemistry professor Aladar Szalay and colleagues at Loma Linda University, Genelux Corp., and the University of Würzburg recently monitored the real-time migration of light-emitting bacteria and vaccinia virus from an injection site to tumor tissue in live animals (*Nat. Biotechnol.* **2004,** *22,* 313–320).

The researchers genetically modified several bacterial strains—including *Salmonella typhimurium*, *Vibrio cholerae*, and *E. coli* with the luciferase gene cluster, and vaccinia with a luciferase–green fluorescent protein (GFP) fusion—so they could monitor the microbes under low-light conditions. They infected healthy mice with the microbes and noted that although the light was initially diffuse throughout the test animals' bodies, it eventually diminished, indicating that the microbes were probably cleared by the host immune system. When the researchers repeated the experiment on mice carrying various tumors, however, they found the microbes quickly took up residence in the tumor tissue, where they flourished.

On closer examination, the researchers detected the microbes first surrounding blood vessels in the tumor region and then spreading from these centers into ever-growing rings throughout the tumor. They speculate that tumor tissue might represent an immunoprivileged environment protecting microbial invaders from attack by a host immune system.

To determine whether the microbes could reenter the bloodstream and infect new tissues, the researchers introduced new tumor tissue to tumor-bearing mice infected with light-emitting microbes. They found that the new tissue did not become infected, suggesting that the initial microbes did not pass back into circulation. However, the new tissues did become infected when new microbes were injected into these mice. The researchers also discovered that the microbes could find small metastatic nodules, which can be difficult to detect otherwise.

On the basis of these last findings, it might be possible to develop a microbe-mediated tumor-specific targeting system as a clinical tool for detecting and removing secondary, as well as primary, tumors. Furthermore, by eliminating concerns about reinfecting healthy tissues, the scientists say, "These systems may allow the development of tumor-specific gene therapy protocols."

—RANDALL C. WILLIS

Manufacturing "plant" against obesity

Dow Chemical and the drug-delivery company NOBEX will co-develop a plant-based peptide, NLC-001, currently in preclinical development as an appetite suppressant to treat obesity.

Under the agreement, NOBEX will provide a gene sequence to be used in combination with Dow Plant Biopharmaceuticals' expression technology. NOBEX will initially evaluate the effectiveness of a plant cell suspension to express NLC-001. If successful, production will be moved to whole plants for rapid scale-up.

"Initial expression in plant cell suspension enables us to evaluate progress months earlier than going directly into whole-plant production," says Radha Krishnan, senior director of chemical development and manufacturing at NOBEX. In addition, the peptide will be conjugated to NOBEX's proprietary polymer technology for oral administration.

The companies anticipate a large market for the peptide and the need for large-volume scalability for clinical trials and future commercialization. The World Health Organization calls obesity a "worldwide epidemic". Yet only in the past 20 years has the condition been more firmly linked to co-morbidities with cancer, hypertension, cardiovascular disease, and diabetes. Scientists and physicians are realizing that obesity is a serious medical condition rather than just a cosmetic concern.

According to the National Institutes of Health, "Obese individuals have a 50–100% increased risk of death from all causes." And the Centers for Disease Control and Prevention say that obesity may soon overtake tobacco as America's number one cause of preventable deaths.

Not only has this provoked an intense public response, but it also is motivating drug manufacturers. Front Line Strategic Consulting estimates that anti-obesity drugs will generate sales of $520 million by 2008.

Dow believes its production technology can help meet these market needs. "More companies today are looking for alternative expression methods to traditional means. We believe our plant-based methods can provide real advantages," says Carolyn Fritz, Dow general manager for industrial biotechnology. Financial terms of the collaboration are not being disclosed, but both parties are contributing resources.

—KIMBERLY S. CLEAVES

PHOTO: COURTESY OF THE FDA

McClellan

McClellan: Some parting thoughts

President Bush's appointment of former FDA Commissioner Mark McClellan to run the Centers for Medicare & Medicaid Services came as a bit of a surprise. McClellan's departure from the FDA, after just 15 months on the job, prompted leading figures in the pharmaceutical industry to say what they really think of him.

It turns out they like him, a lot.

"Commissioner McClellan wasted no time in setting a new course for the FDA, one which is committed to new drug innovation by removing unnecessary regulatory barriers," says Biotechnology Industry Organization (BIO) President Carl Feldbaum.

Alan Holmer, president and CEO of the Pharmaceutical Research and Manufacturers of America (PhRMA), calls McClellan "a capable individual whose initiatives at the FDA have helped bring safe medicines to patients sooner."

These comments reflect McClellan's efforts, since he took the FDA's helm in November 2002, to improve the drug application review and approval process. His policies are primarily laid out in an agency-wide initiative announced in January 2003. It commits the FDA to substantial cuts in drug approval times and incorporating up-and-coming technologies into the review process.

McClellan's approach "sets a new standard for FDA commissioners," stresses Kenneth Kaitin, director of the Tufts University Center for the Study of Drug Development. Kaitin considers McClellan the most effective commissioner to date because "he looks at the pharmaceutical challenge as a public health issue," not as a battle of wits between regulators and industry.

The Generic Pharmaceutical Association (GPhA) underscored a similar theme in its praise of McClellan—a rare demonstration of harmony with BIO and PhRMA.

"Knowledgeable, thoughtful, pragmatic, and fair," is how Kathleen Jaeger, president and CEO of GPhA, describes him. "He has kept the best interests of the nation's public health at the forefront of his decision-making," Jaeger notes.

Lester Crawford, the deputy commissioner under McClellan, is now the FDA's acting commissioner. It is unknown when a new commissioner will be appointed.

"We've been through a little bit of a honeymoon period, where McClellan has really headed the FDA very effectively," said G. Steven Burrill, CEO of Burrill & Co., in a talk accompanying the release of his 18th annual biotech industry report. "I think we are going into much less certain times."

—DAVID FILMORE

Reporting race?

Adding race and ethnicity reporting requirements to FDA MedWatch forms will be expensive, of little use, and inconsistent with the global nature of the pharmaceutical business, industry representatives say.

MedWatch was established in 1993 to allow health care professionals and consumers to report adverse drug events. In December 2003, the FDA proposed amending the reporting forms to include fields for race and ethnicity data.

Regulations require postmarket adverse event data to be analyzed according to demographic subgroups, the agency says. But because there are no specific, searchable boxes for race and ethnicity, it is difficult to assess events on the basis of these considerations. The FDA proposes using standardized race and ethnicity categories recommended by the Office of Management and Budget (OMB).

PHOTOS: PHOTODISC

In response to calls for comment on the FDA's proposal, the National Medical Association, which represents U.S. physicians of African descent, expressed its support. "The NMA is concerned that the paucity of clinical data provided to physicians may be one of many factors contributing to disparities between whites and minorities," wrote Randall Maxey, president of the organization.

Donald Black, vice president of global strategic regulatory development at Merck, however, warns in his comments that the OMB standards were designed explicitly for collecting race and ethnicity data in the United States and are not appropriate in an international setting. "Because pharmaceuticals are marketed worldwide, adverse event information is global in scope," he writes.

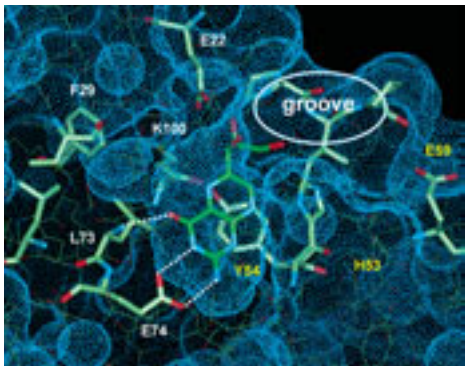
Gillian Woollett, who heads up science and regulatory affairs at BIO, agrees. BIO, she writes, "is concerned that this effort is not consistent with the FDA's goals of harmonization with regulatory bodies in other countries."

Both Black and Woollett also agree that reporting racial and ethnic categories will be of little, if any, value in producing scientifically defensible conclusions, because the categories lack "sufficient definition".

Industry executives worry about the costs associated with this proposed change as well, as it would require companies to revise their data collection software and, Woollett suggests, to set up separate systems in different countries.

Whatever the agency decides, Woollett suggests that this proposal not be considered until the FDA finalizes its draft guidance (*www.fda.gov/cber/gdlns/racethclin.htm*) on collecting race and ethnic data in clinical trials.

—DAVID FILMORE



In the groove. Model of a compound bound in the active site of DHNA. On the top right is an unoccupied groove that could be accessed to increase the potency of inhibitors. (Adapted with permission from Sanders, W. J.; et al. *J. Med. Chem.* **2004,** *47,* 709–718.)

Crystal concerns

Researchers at Abbott Laboratories, using high-throughput X-ray crystallography fragment screening to uncover potent inhibitors of an antibacterial target, obtained a result, they say, that "clearly illustrates a potential problem with crystallographic screening and structure-directed drug design."

Abbott researcher William Sanders and colleagues identified dihydroneopterin aldolase (DHNA) as a promising target for selective antibiotics, because the enzyme is conserved across bacterial species but doesn't exist in humans. They used Abbott's CrystaLEAD method to identify DHNA inhibitors (*J. Med. Chem.* **2004,** *47,* 709–718).

The researchers screened a 10,000-compound library against the DHNA crystal structure, using a crystal soaking method and electron density mapping. They identified two compounds that bound DHNA and, in enzymatic assays, were shown to be competitive inhibitors (IC_{50} of 28 and 80 µM).

They likewise screened a urokinase inhibitor library and identified another DHNA ligand (IC_{50} of 50 µM).

Because these ligands shared a common substructure, the scientists could perform a targeted enzymatic inhibition screen. They found even more potent inhibitors, with several hits having IC_{50} values on the order of 1 µM. However, using the crystal soaking method, they could not obtain crystal structures with DHNA for these compounds.

Through cocrystallization experiments, Sanders and his team concluded that the binding of these compounds requires "a conformational shift that cannot occur in the crystal lattice." Binding in an extended groove adjacent to the primary active site, they say, triggers this shift.

On the basis of surface area models of DHNA, they chemically extended their initial hits to access the binding groove and found several structures with significantly enhanced enzyme inhibition. However, none of the structures could actually inhibit bacterial growth, including species of *Staphylococcus*, *Streptococcus*, and *Haemophilus*.

This negative result aside, the scientists noted that potential leads were possibly overlooked in the original CrystaLEAD screening, highlighting a shortcoming of the growing field of crystal structure-based drug discovery. "While the crystalline state of an enzyme may select primarily for favorable conformations among compounds within a screening library," they report, "the soluble enzyme can have entirely different requirements."

—RANDALL C. WILLIS

Toward population proteomics

Researchers at Intrinsic Bioprobes, Inc., have devised a new approach for the high-throughput screening of selected proteins.

First-generation proteomic technologies—2D gel electrophoresis, LC, and MS—have largely been focused on identifying as many peptides as possible in a single sample. But to understand the complexity of the human proteome, it will be necessary to repetitively and reproducibly screen hundreds or thousands of samples on a simple robust platform. Doing so will allow researchers and clinicians to define a "normal" human proteome against which they can identify disease-associated biomarkers.

Intrinsic Bioprobes scientist Dobrin Nedelkov and colleagues have developed such a platform that combines mass spectrometric immunoassay (MSIA) and bioreactive mass spectrometer probes (BRPs). MSIA relies on microliter-volume affinity capture of selected proteins in pipette tips and the elution of the proteins onto BRPs, where they are digested by surface-immobilized enzymes such as trypsin. Although the researchers initially devised their system for small-scale analyses, they have more recently demonstrated its high-throughput capabilities by performing parallel processing of 96 plasma aliquots using a Beckman Multimek 96 pipetting workstation (*Anal. Chem.* **2004,** *76,* 1733–1737).

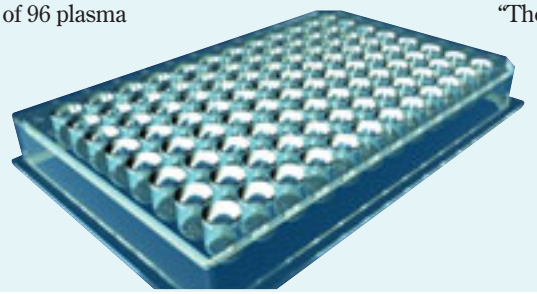


ILLUSTRATION: TONY FERNANDEZ

Initially, the researchers probed the samples for transthyretin (TTR), a plasma protein that is associated with a number of disorders involving amyloid deposition in the peripheral nerves and heart. Using their system, they were able to process 96 identical plasma samples in less than 90 min, extracting protein using anti-TTR affinity tips. By performing a database search, the researchers identified each spectrum as belonging to TTR and found an additional signal that corresponded to a cysteinylated peptide fragment, a common post-translational modification.

They then repeated their experiments by extracting samples with antitransferrin tips to ensure that the approach would work with disulfide cross-linked proteins. Carbohydrate-deficient transferrin is prevalent in cases of excessive alcohol consumption and is used as a clinical marker for chronic alcohol abuse. The researchers could identify transferrin mass spectra from all but one of their samples, but the sequence coverage was somewhat lower than in the TTR experiments—largely the result of carbohydrate-containing peptides and those outside the mass spectral window studied.

Given these results, the researchers say, "The approach has significant potential as a protein-phenotyping method for small- to moderate-sized proteins."

—RANDALL C. WILLIS ■