PHOTO: IBM

Kovac is heading up a new health care initiative at IBM.

IBM activities

IBM's information technology platforms, already entrenched in life science research, have recently made significant inroads in integrating drug discovery efforts, following the company's announcement of a $250 million global health care initiative in February.

IBM and Affymetrix embarked on a joint program in March to combine Affymetrix's GeneChip and IBM's professional services to aid global research activities.

The companies are promoting open standards and new protocols for cross-organizational and cross-disciplinary integration of patient information with genomic research data. The program has already attracted several groups including the Mayo Clinic, the H. Lee Moffit Cancer Center & Research Institute, and the Federation of Clinical Immunology Societies (FOCIS). "The integration of different types of data from different member FOCIS centers is crucial for our group to study diseases across organ and disease boundaries," says Garry Fathman, professor of medicine at Stanford University and chairman of FOCIS. "The collaborative work that FOCIS is doing, and which this IBM–Affymetrix initiative is enabling, represents the future of research in immune-mediated diseases."

Also in March, the business software and services company SAS introduced its drug development software on an IBM infrastructure.

SAS previously announced that Bristol-Myers Squibb (BMS) would be using another IBM-powered product, Scientific Discovery Solutions, to improve scientific collaboration.

As part of its new health care initiative, IBM will also be creating the IBM Research Healthcare and Life Sciences Institute, a new "clinical transformation" consulting practice, and an "information-based medicine" business unit.

"IBM is deeply committed to developing the on-demand solutions and offering the consulting expertise and business insights that can help the health care industry transform," says Caroline Kovac, general manager of IBM Healthcare and Life Sciences. "We can help bring catalytic change."

—DAVID FILMORE

Inhibiting autoimmunity

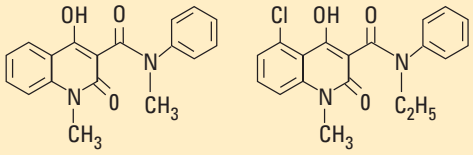
Scientists at Active Biotech, a Sweden-based drug discovery company, recently reported on their efforts to optimize roquinimex, a previously failed therapy candidate for multiple sclerosis (MS).

Pharmacia & Upjohn, now part of Pfizer, halted Phase III MS studies of Linomide (roquinimex) in 1997 because of unacceptable toxicity. However, the compound's ability to inhibit experimental autoimmune encephalomyelitis (EAE) in mice and rats—a model system for human MS—and its early promise in human studies make it an advantageous starting point for MS drug design.

To improve the compound for future therapeutic use, Stig Jönsson and colleagues from Active Biotech generated numerous chemical derivatives of roquinimex and determined structure–activity relationships (SARs; *J. Med. Chem.* **2004,** *47,* 2075–2088). They screened the new compounds for activity against EAE and tested the most active ones for proinflammatory responses in beagles.

The researchers used four substituent classes—alkyls, halogens, acceptors, and donors—to generate derivatives of roquinimex at several positions. First, they made modifications at the 5-, 6-, 7-, and 8-positions of the quinoline ring (R_1), finding that EAE potency was enhanced by substitutions at the 5- and 6-positions but not the 7- and 8-positions, with the 5-position changes showing the greatest effects. At the *N*-carboxamide position (R_2), the researchers determined that only the endogenous methyl substitution was effective.

In substituting the methyl group of the *N*-carboxamide position (R_3) for longer alkyl chains, they noted that the EAE activity dropped in all cases, although only modestly for the change from methyl to ethyl. Similarly, the researchers found that substitutions at the para and meta positions of the 3-carboxamide phenyl ring (R_4) had little effect on EAE activity, whereas changes at the ortho position had an adverse influence.



Roquinimex Laquinimod

Before and after. Active Biotech hopes laquinimod will fare better in clinical trials for MS treatment than roquinimex did.

The researchers then examined the ability of some compounds with high EAE activity to trigger a proinflammatory response in dogs. They found that derivatives substituted at the R_1 6-position exhibited a proinflammatory response. Likewise, they determined that compounds substituted at the R_1 5-position showed a proinflammatory response when R_3 was a methyl group but not when it was substituted for an ethyl group.

This led to the discovery of laquinimod, a candidate with improved potency and a better toxicological profile than roquinimex, according to the researchers. The compound is currently in Phase II studies for the treatment of MS.

—RANDALL C. WILLIS

On the critical path

Innovation or stagnation? This is the challenge the FDA posed to itself and to all participants in the drug development process in a white paper released in March.

The report (*www.fda.gov/oc/initiatives/criticalpath/whitepaper.html*), in essence, examines the much maligned "pipeline problem"—that is, the recent slowdown in innovative medical therapies reaching patients. The number of applications submitted for new molecular entities and novel biologics has steadily decreased over the last 5–6 years, according to the agency, whereas pharmaceutical R&D spending has almost doubled in that time.

The fundamental issue identified by the FDA—what it calls a "growing crisis"—is that product development is not keeping pace with basic science innovation.

"With so much promising technology in development in the clinical labs, ranging from engineered tissues to new kinds of biologicals and genomics-based treatments, we need to turn the process of bringing these technologies to patients from a costly and time-consuming art form to a well-understood science," says Mark McClellan, former FDA commissioner and current Centers for Medicare & Medicaid Services administrator.

There is an urgent need, the report stresses, to concentrate on "critical path research" directed at improving the product development process.

This, the agency believes, will primarily require new evaluation tools—such as computer-based models, genomic and proteomic biomarkers, and novel clinical protocols—focused on more efficiently ensuring product safety, demonstrating medical utility, and attaining mass-produced product. To provide concrete and specific recommendations, the FDA plans, in the short term, to create a "critical-path opportunities list" prioritizing the most pressing development problems and identifying areas most likely to experience quick improvements and have the largest public health benefits.

FDA "researchers have a unique vantage point on scientific challenges that cause

PHOTO: PHOTODISC

delays and failures in product testing and manufacture," McClellan says. The "opportunities list" is meant to be only the first broad step in an extensive process involving cooperation between the agency, industry, and academia. The biotechnology industry, at least, says it is ready for the challenge.

"This is a courageous statement from a government agency recognizing the serious problems that are preventing new, innovative drugs and biologics from getting to the patients who need them," says Carl Feldbaum, president of the Biotechnology Industry Organization (BIO). "BIO is pleased to work with the FDA to develop those tools necessary to streamline and improve the product development process."

—DAVID FILMORE

FDA: Increasing interaction, selectively

The FDA has selected at least seven drug candidates now in clinical testing for a new program designed to test the effectiveness of enhanced interaction between sponsors and the agency in improving the Investigational New Drug phase of development.

The Continuous Marketing Application (CMA) Pilot 2 program, mandated in the June 2002 reauthorization of the Prescription Drug User Fee Act, directs each of the agency's drug review divisions to pick one product to receive continuous guidance and feedback from the FDA as it moves through its clinical track. Each candidate, according to the FDA, must already be designated a fast track product and should be selected on the basis of its potential public health impact and chances of benefiting from concentrated scientific and regulatory dialogue.

"We are honored to have been selected for inclusion into this exclusive and pioneering program," says Hank Fuchs, president and CEO of IntraBiotics Pharmaceuticals. The FDA Division of Anti-Infective Drug Products chose the company's lead product iseganan, an oral solution for the prevention of ventilator-associated pneumonia that recently entered the first of two planned Phase III trials, for the Pilot 2 program.

The Division of Oncology Drug Products selected as its Pilot 2 candidate Millennium Pharmaceuticals' MLN2704, an immunoconjugate currently in Phase I/II trials for treating patients with prostate cancer. "Our participation in the Pilot 2 program may further speed and clarify the regulatory path for this important molecule," says Robert Pietrusko, senior vice president of worldwide regulatory affairs and pharmacovigilance at Millennium.

Human Genome Sciences' LymphoStat-B for systemic lupus erythematosus, NeoPharm's anticancer drug IL 13-PE38QQR, and Discovery Laboratories' Surfaxin, a humanized surfactant technology for the treatment of acute respiratory distress syndrome, were also publicly announced by the companies as Pilot 2 selectees. Discovery Laboratories submitted a New Drug Application to the FDA for Surfaxin in April.

The agency indicates that two other products have also been chosen for the program. Nine divisions, which have yet to select candidates, will be taking applications until September 30.

The agency has, on a limited basis, engaged in early review of marketing applications in the past, but there has not previously been a formal program to assess the value and costs of such activities. Throughout its duration, an independent consultant will evaluate the CMA Pilot 2 program, along with a concurrent, less selective, and less interactive Pilot 1 program.

The precise nature of the feedback and interactions will be laid out in individual agreements between each drug sponsor and the FDA.

—DAVID FILMORE

Meeting for minds

Chemical Diversity Labs and the Laboratory for Drug Discovery in Neurodegeneration (LDDN) at Harvard Medical School are collaborating to discover new tools for understanding and treating neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, ALS (Lou Gehrig's disease), multiple sclerosis, and Huntington's disease.

Under their agreement, Chemical Diversity will use its small-molecule collection and Chemosoft in silico software to select a maximally diverse set of compounds for biological screening against LDDN's neurodegenerative disease targets. LDDN will in turn provide Chemical Diversity with screening data for creating second-generation libraries.

"Effective drugs for diseases of the central nervous system are especially difficult to develop, due to the complexity of the brain as well as its physical isolation by the blood–brain barrier," says Ilya Okun, vice president of research and development at Chemical Diversity. "We see our collaboration with LDDN as an important source of de novo biological data to direct exploratory synthesis of chemical library systems for the central nervous system area."

LDDN is a major initiative of the Harvard Center for Neurodegeneration and Repair, a decentralized community of Harvard Medical School-affiliated neuroscience researchers that has created what it calls a "drug discovery engine" comprising assay development, high-throughput screening, informatics, and exploratory medicinal chemistry.

"The goal of the LDDN is to transform basic neurobiological findings into drug discovery programs through the discovery of new chemical compounds that have promise as research tools or as novel therapeutics for neurodegenerative disorders," says LDDN director Ross Stein. Establishing partnerships with biopharmaceutical companies is an important part of the Harvard group's strategy to commercialize its drug candidates.

Financial terms of the agreement with Chemical Diversity were not disclosed. The current neurodegenerative drug market is approximately $30 billion.

—DAVID FILMORE

Profiling Parkinson's

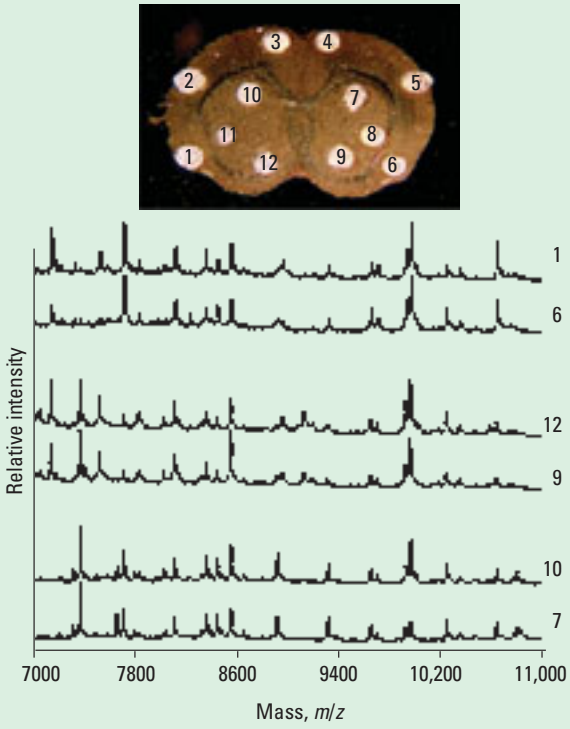
Per Andrén and colleagues at Uppsala University, Vanderbilt University, and the Karolinska Institute recently uncovered molecular events behind Parkinson's disease by using matrix-assisted laser desorption/ionization (MALDI) MS. Unique MS protein profiles can be obtained in specific brain regions to study complex biochemical processes, the researchers say.

Parkinson's is a common disease caused by selective degeneration of dopaminergic neurons in the brain. In the early stages of the disease, the administration of the dopamine precursor L-Dopa or dopamine receptor agonists can alleviate symptoms such as rigidity, imbalance, and tremor. However, the precise metabolic events in people with the condition are poorly understood. (*J. Proteome Res.* **2004,** *2,* 289–295).

The researchers mimicked human Parkinson's in rats by administering the neurotoxin 6-hydroxydopamine (6-OHDA) to one side of the brain. They then sacrificed the animals and treated tissue sections for direct MS analysis. In a typical experiment, the scientists detected 200–300 protein and peptide signals ranging in size from 2 to 25 kDa. They found that these profiles were highly reproducible between consecutive brain sections and between equivalent regions of a single section.

The researchers compared the protein and peptide profiles of 6-OHDA-treated brains with and without L-Dopa administration. They found that although many MS peaks were similar between the two samples, there were distinct differences. For example, the level of a cytochrome c oxidase subunit, a metabolic marker of neuronal activity, was significantly lower in the dopamine-depleted brain than in the side treated with L-Dopa. Likewise, they noticed decreased levels of cytochrome c, an apoptosis-related marker, in non-L-Dopa-treated sections.

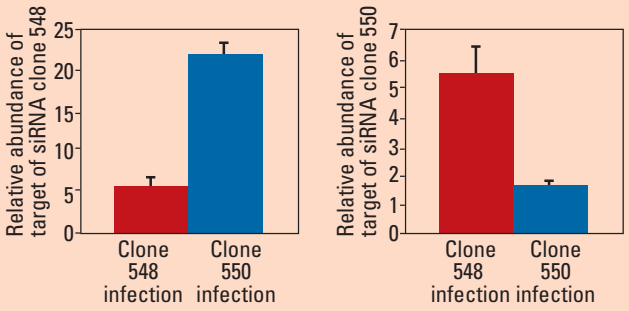
Aside from the identified markers, the researchers noted a variety of other peaks they are investigating. Similarly, they noted several changes in post-translational modification patterns between the samples, which might give some clue about the metabolic changes occurring in the dopamine-depleted and L-Dopa-treated samples.



Left brain, right brain. Researchers performed direct MALDI MS analysis of brain sections to determine marker profiles of Parkinson's disease. (Adapted with permission from Pierson, J.; et al. *J. Proteome Res.* **2004,** *2,* 289–295.)

"Our results showed that MALDI MS protein profiling directly on tissue sections provides unique information regarding the peptide and protein expression in experimental models of Parkinson's disease," the authors write. "The MALDI MS profiling may give a better understanding of the underlying pathophysiology."

—RANDALL C. WILLIS



Expression suppression. Using siRNAs, researchers could limit the expression of specific target genes in mammalian cells. (Adapted with permission from Luo, B.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101,* 5494–5499.)

SPEEDy siRNA

In theory, it should be possible to use small interfering RNA (siRNA) libraries to perform genomewide functional screens, but the chemical synthesis of the thousands of oligonucleotides required is time-consuming and cost-prohibitive. Harvey Lodish and colleagues at the Whitehead Institute for Biomedical Research and the Massachusetts Institute of Technology recently developed what they report to be a simple, effective, and inexpensive method for constructing siRNA expression libraries from cDNA templates (*Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101,* 5494–5499). They called their method "siRNA production by enzymatic engineering of DNA," or SPEED.

The SPEED procedure can be roughly broken into four steps. First, the researchers digest a cDNA library with five specific restriction enzymes and ligate the resulting fragments to a hairpin linker. They then convert the extended hairpins into palindromic DNA molecules by ligating a primer fragment to the molecule and replicating the hairpin portion, resulting in two palindromic cDNA sequences separated by a double-stranded hairpin.

The scientists then clone the palindromic fragment into a retroviral vector, and remove the original hairpin section. Thus, when they transcribe the palindromic cDNA sequence with RNA polymerase, they generate a hairpin siRNA molecule.

The researchers used the SPEED method to develop an siRNA library from a mouse embryo cDNA library, obtaining 3 million clones. They then transformed cell lines with five of the clones and showed, using Northern blot analysis, that each cell expressed the appropriate siRNA.

Furthermore, the researchers found that the siRNAs could specifically and potently inhibit expression of the corresponding endogenous gene.

The team is confident their method can be extended to other libraries.

"For example, SPEED can be used to provide a library of siRNAs that target different segments of a viral genome such as HIV," the authors write. "Screening of such a library for siRNAs that potently inhibit virus replication or other viral-encoded functions could identify potential siRNA-based therapeutics."

—RANDALL C. WILLIS

Delivering a nuclear payload

Researchers at the NIH, Ciphergen BioSystems, and Boston University have developed a radionuclide delivery system based on sequence-specific peptide nucleic acids (PNAs).

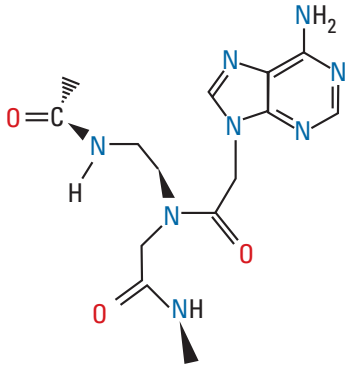
Although radiotherapy has played a significant role in treating diseases such as cancer, an inherent drawback is that it tends to destroy good cells as well as the bad ones. By targeting specific cancer-related genes, however, clinicians might be able to circumvent this problem.

Researchers can target gene sequences using an antisense approach, relying on sequence-specific oligonucleotides to deliver radionuclides such as ^{125}I, ^{123}I, or ^{111}In. Unfortunately, oligonucleotides can be very sensitive to nuclease degradation. PNAs are more chemically and biologically stable than oligonucleotides because they carry a polyamide backbone instead of a sugar–phosphate backbone.

To assess the effectiveness of PNA delivery, Igor Panyutin of the NIH and his colleagues conjugated the metal-chelating reagent DTPA to free amino groups on a PNA and a DNA molecule, both with the same nucleotide sequences (*Eur. J. Nucl. Med. Molec. Imaging* **2004,** in press). Using surface-enhanced laser desorption/ionization (SELDI) MS and HPLC, they noted reaction yields of >85%. The researchers then bound ^{111}In to the conjugates.

Using gel retardation assays, they found that the PNA–DTPA–^{111}In complex bound target DNA more efficiently than the DNA–DTPA–^{111}In complex.

Similarly, the scientists determined through DNA sequencing that the PNA complex produced a higher yield of target DNA breaks (5.35%) than the DNA complex (1.9%), and that, in both cases, the breaks occurred within the region bound by the PNA and DNA vehicles. Furthermore, by increasing the number of DTPA molecules conjugated to the PNA, they could increase the target break yield to almost 7%.



A peptide nucleic acid.

Although these studies were performed with only one PNA sequence, the researchers are confident the methods are applicable to a variety of target sequences. Similarly, they believe their in vitro results indicate in vivo possibilities.

"Recently, there has been significant progress in PNA cellular delivery that has substantially reduced the initial skepticism regarding the therapeutic and in vivo diagnostic use of PNAs," the researchers write. "In addition, due to a neutral backbone, PNA appears to lack general toxicity and nonspecific protein binding."

—RANDALL C. WILLIS ■