As a result, says Thomas N. Salzmann, vice president for chemistry at Merck, "not everyone here is a convert" to combinatorial chemistry—although he adds that the resistance is "not for any good scientific reasons."

Yet even the most ardent advocates of combinatorial chemistry say they will never put traditional organic chemists out of business. "We still need their creativity to develop new chemistry, new reactions that we can use in our brute-force methods," says Jack Baldwin, president of Pharmacopia, a year-old drug discovery company. What's more, combinatorial chemistry has had to cede some tasks to traditional synthetic chemistry because of a practical drawback.

The drawback is that the kinds of molecules best suited to the combinatorial approach—peptides and nucleic acids—can't be taken by mouth; they are either too large to be absorbed in the gastrointestinal tract, or they get digested along the way. To cope with that limitation, officials at some companies, such as NeXagen and Protein Engineering, are targeting diseases severe enough that injections will be acceptable, such as cancer and AIDS. Or they are adopting other goals: using combinatorial libraries for diagnostic purposes (see box) or as guides for traditional chemical synthesis.

"We can use these high-affinity binders not as drugs themselves, but as models from which small organic molecules can be crafted with the appropriate spatial and biophysical characteristics," explains Edward Cannon, Protein Engineering's chief executive officer. By studying the shapes created by combinatorial chemistry, for example, his company has identified the structural features that are the key to inhibiting elastase—an enzyme that plays a role in inflammatory diseases—and several enzymes involved in clotting.

These limits may only be temporary. As combinatorial chemists move beyond nucleic acids and peptides to small organic molecules, they may be able to compete head-to-head with traditional drug discovery techniques. Creating small molecules in combinatorial fashion, says Affymax's Gordon, "is definitely a challenge, but we and many others are finding that small molecule synthesis is doable." Michael Pavia of Sphinx Pharmaceuticals explains that "it's not that it's harder to do with small organics; it's just that we need to develop the ability to do traditional organic chemistry on solid supports."

At Parke-Davis, for example, Sheila Hobbs DeWitt, using the company's DIVERSOMERS technology, has created an array of ringed heterocycles (compounds containing oxygen, nitrogen, or sulfur). Among them are benzodiazepines—the family that includes the drugs Valium and Xanax—and hydantoins, which include Dilantin. Still, Gordon adds, it will probably be a few years before combinatorial synthesis of small molecules rivals the power it has demonstrated with peptides and nucleic acids.

When it does, the main problem combinatorial chemists may face is their technique's very efficiency. Most assay systems are not designed to handle billions of compounds. Then there is the glut of information that comes from testing such a large number of compounds with known structures. "In theory, combinatorial chemistry provides the perfect data set for sophisticated structure-activity relationship analysis," says Merck's Salzmann. In reality, says Chiron's Moos, "we can now generate so much data so fast that we're in danger of becoming overwhelmed." In some respects, combinatorial chemistry may be too much of a good thing.

–Joseph Alper

ATMOSPHERIC CHEMISTRY

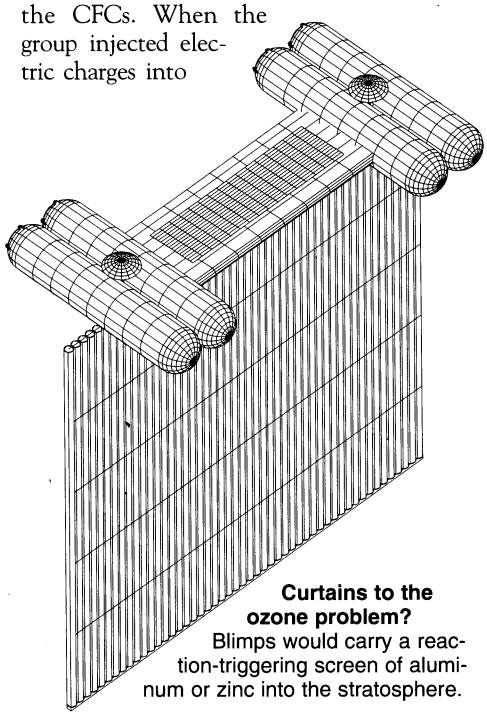
A High-Flying Fix for Ozone Loss

Alfred Wong knows he's in danger of overreaching when he talks about extending his lab-scale chemical reaction to the scale of the globe. But the University of California, Los Angeles, plasma physicist thinks the chemical transformation he has seen in a chamber of gases has implications too important for the global atmosphere to keep silent, in spite of a blast of criticism from atmospheric scientists. Wong's bold claim: Twenty or so panels of zinc or aluminum, each at least the size of a football field, carried aloft by balloons, could sustain a global version of the laboratory process—and provide a quick fix for stratospheric ozone loss.

That implication is buried in a paper in the 9 May *Physical Review Letters*, where Wong and his colleagues describe a scheme for inactivating the chlorine atoms, unleashed by manmade chlorofluorocarbons (CFCs), that destroy ozone in the stratosphere. The paper mainly describes laboratory results, but Wong's grander claim was the subject of a UCLA press release—and ensuing coverage by television networks and print media, including the Associated Press and *Newsweek*. "It was very well received," noted a spokesman in the UCLA press office.

By the press perhaps, but not by atmospheric scientists, who cite daunting technical problems. "It is a very clever idea, but it gets messy," says Earle Williams, who studies atmospheric electrical phenomena at the Massachusetts Institute of Technology (MIT).

Atmospheric chemists have little quarrel with the findings Wong's group described in the paper. In a coffin-sized chamber, the group monitored a simplified stratospheric brew including CFCs and low levels of ozone molecules, which were constantly created by ultraviolet light but were depleted by the CFCs. When the group injected electric charges into the chamber, ozone levels increased sharply. The researchers concluded that, by converting reactive chlorine atoms to virtually inert chloride ions, the charges had stymied the ozone-destroying process.



ALFRED WONG

Curtains to the ozone problem? Blimps would carry a reaction-triggering screen of aluminum or zinc into the stratosphere.

In their paper, Wong and his colleagues limited themselves to raising the possibility that the process could be scaled up, without saying how. But in an interview, Wong spelled out his scheme. Into the Arctic and Antarctic stratospheres, where the worst ozone depletion takes place, he would fly 10 to 20 balloon-borne platforms carrying sheets, wires, or curtains of a metal whose electrons can easily be dislodged by ultraviolet light. As in the laboratory, Wong believes some of the charges would find their way to the reactive chlorine atoms, converting them into inactive chloride ions that could then be collected by other, positively charged surfaces. Wong says he has been working with an engineering firm to draw up plans for the platforms, which would cost $25 million each. The total of $500 million for the full fleet would be a bargain—if it restored the ozone layer.

Some prominent atmospheric scientists don't dismiss the idea of global remediation. "If you have a serious problem [like ozone depletion]...you have to think about remediation," notes F. Sherwood Rowland of the University of California, Irvine, who with Mario Molina, now of MIT, first described the ozone-destroying chemistry of CFCs in 1973. Ralph Cicerone, a colleague of Row-

land's at Irvine, agrees that there could be a place for large-scale "geo-engineering."

But Cicerone knows from experience how easily promising schemes for tinkering with stratospheric chemistry can go bust. Three years ago, he and his colleagues proposed in *Science* that judicious injections of small hydrocarbon molecules such as propane—delivered by a fleet of high-flying tanker airplanes—could shift the complex chemical balance in the stratosphere away from ozone destruction. More recently, however, they reanalyzed the chemistry of this "cure" and found that it would almost certainly exacerbate ozone depletion. Cicerone, along with Rowland and other atmospheric chemists *Science* contacted, believes Wong would be similarly blind-sided.

For one thing, notes Cicerone, Wong and his colleagues had to inject 20 times as many charges into the chamber as there were chlorine species to deactivate. Other molecules must have sopped up the charges, a process Cicerone says "would be an enormous problem" in the real atmosphere. Even if the charges did reach the chlorine and inactivate it, adds Molina, the resulting chloride ions could combine into chlorine molecules; solar radiation could then blast the molecules apart into a brand-new pair of ozone-eating chlorine atoms. "My bottom line," says Cicerone, "is that you could do this [cause ozone recovery] in a few cubic meters of air in a laboratory, but you cannot scale it up" to the real stratosphere.

Wong admits that "a lot more needs to be done" to make his scheme workable—but he stands by it. He is convinced that enough of the charges would have the intended effect to warrant testing the technique in the real world. "I have come up with a concept and proved it in principle," he contends doggedly. But to Rowland, planetary engineers like Wong still have a long way to go. "So far," he says, "no one who has talked about remediation has come anywhere close to having a process that can actually do it."

–Ivan Amato

AIDS VACCINES

Immune Response Corp.—Take Two

Scientific data are difficult to evaluate at huge conferences, especially when the presentation attracts standing-room-only crowds, the klieg-light glare of TV cameras, and stock analysts chattering into cellular phones. That was the scene last July at the international AIDS conference in Berlin when results were unveiled from the first double-blind, placebo-controlled trial of a vaccine designed to treat people already infected with HIV—a "therapeutic" rather than a preventive vaccine.

In that highly charged setting, the data took a beating, as did Immune Response Corp. (IRC), the company developing the vaccine in collaboration with Rhone-Poulenc Rorer Inc. Now, however, an extensive analysis of the trial has been published in the June issue of the *Journal of Infectious Diseases*, and while no one is claiming the vaccine works, many researchers agree with the paper's conclusion: The vaccine's effects appear encouraging—albeit modest—and the studies should be expanded. "It's enticing," says Duke University's Dani Bolognesi. "It's not a wash."

"Now we should try to ignore the hype and the past and look at the data."

—Don Francis

That's a significant turnaround from the reception IRC's therapeutic AIDS vaccine received in Berlin—and before. From the beginning, the project was subject to intense scrutiny, partly because it was launched by IRC board member Jonas Salk, of polio vaccine fame. When Salk proposed the idea in a 1987 *Nature* article, many researchers doubted injecting a vaccine into an infected person would have any effect. "The concept that you could give more antigen [a substance that triggers an immune response] to someone who already has a lot of that antigen and expect biological impact is stretching it," says James Kahn, associate director of the AIDS program at San Francisco General Hospital.

As the paper explains, the study did not evaluate whether the vaccine, an inactivated form of HIV minus the surface protein gp120, can slow the progression of disease and extend the lives of those infected with HIV. Instead, the 1-year trial in 103 healthy, HIV-infected people at nine U.S. sites assessed "surrogate markers" of disease progression such as the decline of CD4s, key white blood cells, and the increase in levels of HIV. "We got consistent [positive] results on all the markers," says Richard Trauger, IRC's chief immunologist on the study and the paper's first author.

Central to the study was a test that measures levels of HIV DNA, or "viral load," in patients' blood cells. This test, which relies on the polymerase chain reaction (PCR), showed that after 1 year, HIV in treated patients increased an average of only 14%, while the amount in controls increased 56%. IRC's François Ferre, who developed this PCR assay, adds that he was particularly impressed that for the first 6 months after the vaccinations, HIV levels in some patients remained stable. The reliability of the assay was criticized in Berlin, but now it has ceased to be a major issue. "I can't find anything particularly wrong with this assay," says Brooks Jackson, who heads the virology committee for the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases (NIAID).

In addition to viral load data, the paper reports that CD4 cells as a fraction of all T lymphocytes—a measure some researchers believe is more telling than absolute CD4 counts—fell only marginally in treated patients (an average of 0.164%) but underwent a moderate drop in controls (5.03%). And the vaccine, which didn't cause any serious side effects, also seems to have boosted the cell-mediated arm of the immune system, which clears infected cells, and boosted some anti-HIV antibody levels. By and large, however, researchers are more interested in the HIV DNA data, because they assume it provides a better measure of disease progression.

Researchers interviewed by *Science* urged that these results be kept in perspective. "I believe the data, but I'm not all that impressed," says David Ho, who heads the Aaron Diamond AIDS Research Center. Jackson, who works at Case Western Reserve University in Cleveland, is of a similar mind. "It may be statistically significant, but it's modest," Jackson says. Then again, he adds, "I didn't think there'd be this much." Others say the data warrant a larger study. "There's something interesting there going on with viral burden, and we need to find out more," says Steven Schnittman, chief of the medical branch at NIAID's Division of AIDS.

Even skeptics like Kahn are getting on board; he is talking to IRC about leading a large-scale trial of the vaccine. "We don't have a lot more to offer, and there's the potential to gain scientific information to move forward," he says. Other researchers are also taking a different tone. Retrovirologist Don Francis of Genentech, who has long been skeptical about therapeutic HIV vaccines, says that although the IRC vaccine "may not be penicillin," he now believes the approach has merit. "We have to throw away the biases engendered in Berlin," says Francis. "Now we should try to ignore the hype and the past and look at the data." The most significant data, of course, would be those showing improvements in life span, and IRC hopes to launch a trial by the end of the year to find out whether the vaccine can delay AIDS symptoms and lengthen life.

–Jon Cohen