Hard choices

Even at this relatively blistering pace, however, 3D structure determination and related structural genomics projects remain too slow and costly to provide an atomic map for all human proteins, at least anytime soon. "Structural genomics is a lot harder than sequencing," says Terwilliger. Whereas the tools used in sequencing can decode virtually any gene, proteins are more finicky. They require more attention to find the right conditions under which they will be expressed, purified, and coaxed into forming a crystal.

That complexity also makes the work expensive—it costs roughly $100,000 to resolve a single protein structure. At that price, researchers may need to be content in the near term with structures for fewer than 10% of the human protein, forcing experts to choose from among their preferred targets. NIH officials say one desired outcome from the pilot centers is technology that would drastically lower the cost of resolving new structures.

So far there is no consensus in academia on which proteins to pursue. One camp, says Terwilliger, aims to resolve the structures of specific unknown proteins to gain clues about their biochemical function. A second emphasizes the need to survey general shapes of proteins by lumping those thought to be similar into families and obtaining the structure of at least one member of each. A third approach seeks structures for as many proteins of a given organism as possible, such as pathogenic bacteria. And a fourth—the approach most similar to conventional structural biology—homes in on proteins thought to be important for understanding diseases and basic biochemistry.

No matter what the strategy, one concern for academics is that few research groups have the expertise to combine all the pieces of a structural genomics effort. "A single investigator really can't do much on his or her own," says Emil Pie, a crystallographer at the University of Toronto. One result is that academic groups that produce proteins are teaming up with others that specialize in crystallography and bioinformatics. One early pilot project that's looking at proteins from a heat-loving archaeon, for example, involves 17 labs at seven institutions, including the University of California, Los Angeles, Los Alamos National Laboratory in New Mexico, and the University of Auckland in New Zealand.

The situation is a bit better in industry because it's often easier for companies to marshal both money and expertise to tackle specific problems. "We have the ability to build [high-throughput] tools that are difficult for the university sector to [build]," says Schultz of Novartis, who also retains an academic appointment at The Scripps Research Institute in La Jolla, California. Another reason, say Shultz and others, is that industrial researchers are more narrowly focused on short-term goals. "We're not looking to define protein fold space," says Tim Harris, president and CEO of Structural Genomix. "We will work on protein families we know are of interest to industry and [on those] we predict they will be interested in." One such example, says Harris, are protein kinases, which regulate information traffic inside cells and have been shown to be involved in a wide variety of diseases such as leukemia.

One big unknown is whether public and private efforts will dovetail or if, as happened with sequencing, the sectors will race each other to bank their data. Harris says he believes the focused industrial work "will complement what the public domain is doing"—namely, going after the big picture of how proteins fold. Others aren't so sure. "We may see a replay of the situation in genome sequencing," says Chris Sander of the Massachusetts Institute of Technology's Center for Genome Research and of Millennium Pharmaceuticals in Cambridge, Massachusetts.

In the genome arena, says Sander, industry has competed with the publicly funded genome project in a scramble for new medicines, diagnostics, and agricultural products. Although Sander believes that this duplication has accelerated the pace of genome research, Terwilliger sees a downside for structural genomics. If industry keeps half of the data secret, he says, "there will be an awful lot of waste and duplication." Asked whether academic groups will have access to his company's structural data, Harris is noncommittal: "We anticipate that at least some of the structures will be available to the public domain."

Next month NIH is sponsoring a meeting at the Wellcome Trust's Sanger Centre for genome sequencing near Cambridge, U.K., to coordinate international financing of structural genomics as well as to address issues surrounding intellectual property and access to data. If all goes as planned, the result will be an agreement akin to one that grew out of a 1994 meeting in Bermuda that helped promote the coordinated international effort to sequence the human genome, says John Norvell, who is heading up the structural genomics program at the National Institute of General Medical Sciences on the NIH campus in Bethesda, Maryland. But even such an agreement is unlikely to give researchers all the help they will need as they travel along the new road of structural genomics.

–ROBERT F. SERVICE

NEWS

Malaria Researchers Wait For Industry to Join Fight

A huge toll of illness and death, a dire need for new treatments, and rapid scientific progress are inspiring researchers to battle malaria. But most drug companies balk at investing in what they see as a Third World disease

By most indicators, the time is right for the pharmaceutical industry to make a major push against malaria. Existing treatments are failing in the face of rising resistance from both the parasite and its mosquito vectors. At the same time, the first results of a major effort to sequence the genome of the parasite have identified some chinks in its armor that could lead to promising new drugs. And there's no shortage of patients: Each year brings as many as a half-billion new cases, including more than 1 million deaths, most among children.

But there's a problem: The drug industry is not interested. Companies need to make money to satisfy shareholders, and as staggering as malaria's toll may be, medicines to combat or prevent malaria do not set an investor's heart beating faster. The obvious target populations live in sub-Saharan Africa and South Asia, where most patients can't afford expensive new drugs. Wealthy tourists from industrialized countries offer a market, but, at $100 million to $250 million annually, it is modest in pharmaceutical terms. "The commercial return is negligible," says Simon Campbell, a retired senior vice president and head of drug discovery at Pfizer Inc., "so it really is not cost efficient for pharmaceutical companies to undertake malaria research on their own." Another major factor keeping companies out of malaria research is insufficient patent protection in the developing world, says Bert Spilker, senior vice president of the Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, D.C. "It is difficult for companies when countries pirate drugs," he says.

Add to those obstacles the declining potency of current treatments and the paucity of drugs in the pipeline, some of which may not pan out, and the result is that some parts of the world may soon have nothing with which to counter the scourge. "It's a paradoxical situation," says Dyann Wirth, director of the Harvard Malaria Initiative. "It's a very exciting

time from a scientific point of view, and yet we don't get enough new drugs to the market."

Resisting capture

A half-century ago, the world seemed poised to deliver malaria a knockout blow. New synthetic drugs such as chloroquine killed *Plasmodium falciparum*—the most deadly of the four malaria parasite species—with few side effects. And insecticides, notably DDT, slashed populations of the *Anopheles* mosquitoes that transmit the disease. But times have changed. Resistance to both drugs and insecticides is rampant in large swaths of the world, bringing malaria back with a vengeance. Indeed, the effectiveness of atovaquone, the latest drug in the arsenal, began to wane even during the course of its first human trials. Meanwhile, attempts to create a vaccine have proved vexingly difficult, and another hopeful approach—replacing natural mosquito populations with new ones unable to transmit the disease—is still a long way off.

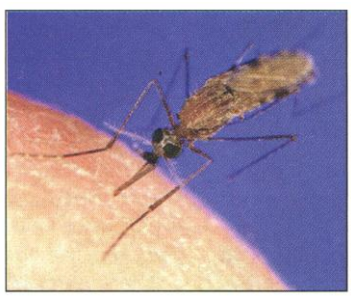
Lives in the balance. Researchers look for help from industry in the battle against malaria, a threat to millions of children in Africa and Asia.

One factor behind widespread drug resistance is that doctors typically treat malaria with one drug only, making it relatively easy for the parasite to adapt. To combat resistance, researchers say they will have to rely more on drug combinations, much like the cocktails that hold down HIV. For instance, Glaxo Wellcome Inc., which is marketing atovaquone, has combined it with an older drug, proguanil, to increase its life-span. (The combination, given the brand name Malarone, has hit the market in 30 countries.) "Perhaps we wouldn't be in such a state today if we had started with combination therapies [earlier]," says Daniel Goldberg, a malaria researcher at Washington University in St. Louis.

Until now, discovering new malaria drugs was a fairly haphazard process. Many of the drugs available today were found by producing and testing countless chemical variations of quinine, a compound from *Cinchona* tree bark that has been known for centuries as an effective antimalarial. Members of this group, including mainstays like chloroquine and mefloquine, all have a chemical structure called quinoline, or one that's closely related. Most are thought to kill the malaria parasite as it's breaking down and gobbling up hemoglobin—a protein complex that transports oxygen—inside red blood cells. Chloroquine and quinine, for instance, block the removal of heme, a byproduct of hemoglobin degradation that is toxic to the parasite. As a result, heme heaps up, poisoning the organism in its own waste.

Researchers are still adding members to the quinine-based drug family. For instance, the Walter Reed Army Institute of Research in Silver Spring, Maryland, the source of most recently developed drugs, has developed a compound called tafenoquine, which effectively kills parasites that have become resistant to multiple other drugs. Tafenoquine is about to enter phase III trials in a collaboration with SmithKline Beecham. But scientists don't expect to discover many more related compounds. "The quinoline structure is pretty much exploited," says Colonel Wilbur Milhous, director of Walter Reed's division of experimental therapeutics.

Over the past decade, some researchers have turned to another naturally occurring compound. In 1972, Chinese scientists isolated the active ingredient (called artemisinin) from *Artemisia annua*, or sweet wormwood, a plant that had been used locally to treat malaria for more than a century. Since then, factories in Southeast Asia, where resistance problems are the most pressing, have started growing *Artemisia* and treating patients with artemisinin on a large scale. The exact mechanism is unknown, but researchers think artemisinin may kill *Plasmodium* because it produces free radicals when it binds to heme; these may damage the parasite's proteins and the lipids in its membrane. Again, they are trying to exploit this trait further by synthesizing a host of similar compounds in the lab and testing their antimalarial activity. The Walter Reed Institute, for instance, has patented a stable, water-soluble derivative called artelinic acid and is testing its efficacy in animals.



Targeted research. Scientists hope that sequencing the *Plasmodium falciparum* genome will also help them interfere with the transmission cycle of the deadly parasite by the *Anopheles* mosquito.

A higher gear

Other researchers are following a different path. Instead of building on compounds known to work, even if the mechanism is unclear, they are searching for enzymes that are unique to the parasite and then producing compounds tailored to thwart them. For instance, Goldberg's group at Washington University has taken a closer look at the breakdown of hemoglobin, a process that requires the activity of protein-chopping enzymes called proteases. The group has identified and determined the three-dimensional structure of three such proteases—called plasmepsins—each of which seems to have a specific role in bringing the giant hemoglobin complex to its knees.

To find inhibitors for the plasmepsins, which would effectively starve *Plasmodium* rather than poison it, Goldberg has teamed up with Jonathan Ellman, a chemist at the University of California, Berkeley. Ellman specializes in combinatorial chemistry, a technique in which researchers use robots to produce tens of thousands of new chemical variations on a theme—in this case, a small molecule that has about the right size and shape to block plasmepsins. Each of the new molecules is then screened for its ability to bind to a plasmepsin. The most promising candidates have been tested in a mouse version of malaria "with some hopeful results," says Goldberg.

Recently, the search for proteases has shifted into higher gear, thanks to the Malaria Genome Project. Sequencing machines at the Sanger Centre in the United Kingdom, The Institute for Genomic Research in Rockville, Maryland, and Stanford University in Palo Alto, California, have been working for 3 years to crack the entire 30-million-base genome of *Plasmodium falciparum*. A rough draft is expected by the end of this year. In sifting through the data released so far, Goldberg says he has already found what look like the genes for several other proteases. "We're eagerly pursuing them," he says.

He's not the only one keeping an eye on

CREDITS: (TOP TO BOTTOM) AP PHOTO/KAREL PRINSLOO; CDC

the daily data flow. Last year, Ewald Beck and his colleagues at Justus Liebig University in Giessen, Germany, found that *Plasmodium* has two enzymes belonging to a pathway that plants and bacteria use to produce isoprenoids, a group of compounds that includes cholesterol. Because this biochemical route, called the DOXP pathway, doesn't occur in humans, the researchers realized that the enzymes made interesting drug targets. While looking for a drug that might block one of the enzymes, the group hit upon fosmidomycin, an antibiotic developed by a Japanese company in the 1970s that never made it to the market. A recent report (*Science*, 3 September 1999, p. 1573) found that fosmidomycin was effective in mice; clinical trials in Africa are next, says Beck. Meanwhile, the group is trying to find even more enzymes along the DOXP pathway.

Discoveries such as Beck's, which would have been impossible without sequence data, are exactly what Malaria Genome Project researchers were hoping for. "That paper in *Science* warmed my heart," says Richard Hyman, who leads the sequencing effort at Stanford. Adds Goldberg: "All of a sudden we have a wealth of targets that we can choose from. It will be an enormous boon to drug development."

Reducing the risk

But new drugs won't help much if they aren't economically viable. One way to hold down costs, researchers say, is to hitch a ride on work under way to combat other, more profitable, diseases. Atovaquone, for example, was developed as a cure for *Pneumocystis* lung infections in AIDS patients. Indeed, "if an old drug is found to have some activity in malaria, I can personally guarantee the companies would fight each other to license it," says PhRMA's Spilker. Similarly, the development of drugs based on the DOXP pathway may be helped by the fact that the same pathway occurs in microbes that plague residents of industrialized countries, such as *Escherichia coli* and *Helicobacter pylori*. In fact, that prospect helped lure investors to a company Beck and co-workers started to further develop fosmidomycin and other drugs. "Our strategy," Beck says, "was to tell them we will find a lot of new antibiotics against very critical bacteria."

Another strategy is to prepare the ground for industry. That means identifying interesting leads and turning them into candidate drugs by doing animal, human safety, and small-scale efficacy tests. The goal is to minimize risk for any company interested in capitalizing on the results. "You have to have [the drug] ready to go without any problems," says Walter Reed's Milhous, "before a company will jump in." For many years Walter Reed handed out such compounds for free, as the government had no procedures to share royalties; Hoffmann–La Roche, for instance, didn't pay for the rights to mefloquine in the 1980s. Today, says Milhous, the institute asks for a percentage of the proceeds of newly developed drugs.

Enticing industry to step in by curbing its financial risks is also the philosophy behind the Medicines for Malaria Venture (MMV), a foundation sponsored by the World Health Organization and several governments and nongovernmental organizations. MMV funds academic researchers with promising drug-discovery projects and tries to hook them up to companies. The companies, in turn, help out with support in kind, such as advice and access to chemical libraries. Founded last year, MMV has an annual budget of about $4 million and is currently supporting three research collaborations in which academics work with Glaxo Wellcome, SmithKline Beecham, and Hoffmann–La Roche. Its goal is a budget of $30 million, says MMV director Robert Ridley, enough to generate one new malaria drug every 5 years.

Although industry may be reluctant to undertake malaria research on its own, initiatives like this help to get it on board, says former Pfizer executive Campbell, who volunteers as chair of MMV's scientific advisory panel. "The industry will do everything possible to help in kind, to offer advice, et cetera," he says. "They're delighted to hear about this initiative. Whenever I talk about it, people's ears prick up."

Some, such as Harvard's Wirth, think it's time for the government to step in, perhaps with tax breaks and longer patents for certain drugs on the condition that the revenue be used for new antimalarials. "The industry recognizes this [disease] as a problem, but it's not going to move without some sort of incentive," says Wirth. "And with so many great drug targets on the horizon, it's critical that we somehow come to grips with this."

–MARTIN ENSERINK

NEWS

U.S., Europe, Japan Look to Speed Up Drug Reviews

Drug companies are hoping to save time and money by submitting the same safety and efficacy data to regulators in the three leading global markets

TOKYO—Why did the Japanese government take more than 30 years to approve "the pill" and only 6 months to OK Viagra, a drug for male impotence? Some blame cultural attitudes toward women for the snail's pace acceptance of the oral contraceptive and decry a double standard. Others say that the answer is not sexism but rather the first fruits of a little-known international effort to streamline the drug review process. This fall, if all goes well, officials from the United States, Europe, and Japan will agree on a common application form in hope of speeding the delivery of other new treatments and, perhaps, lowering the cost to consumers.

Team effort. Japan's Osamu Doi looks forward to global regulations for drug approval.

CREDIT: D. NORMILE

The expected agreement is part of a 10-year-old reform project in the three regions that is known as the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). "Harmonization" makes it possible for regulators in one country to review more quickly safety and efficacy data already submitted to another country. Although the ICH has drawn little attention, it could have a big impact on consumers. "Drugs should be able to reach larger populations faster because a company can do studies and meet the requirements of all three regions," says Sharon Smith Holston, deputy commissioner of the U.S. Food and Drug Administration (FDA). The streamlined format, she says, should also result in "lower costs, because [companies] are not doing multiple [repetitive] studies."

Since 1990, a select group of bureaucrats, drug executives, and academics from the United States, Europe, and Japan have gathered at ICH conferences every other year to identify differences in regulatory approaches and hammer out common standards. They have produced and adopted, at last count, 37 guidelines covering almost every conceivable detail of pharmaceutical development, from the design of clinical trials to the interpretation of statistics. The guidelines have been intro-