Can "chemobrain" be mitigated?

Have you ever locked your keys in the car? Forgotten an appointment? Sure, everyone has memory lapses from time to time. But for some cancer patients who undergo chemotherapy, such slips happen all too often. "Chemobrain," as patients call the condition, is characterized by memory problems, trouble concentrating or multitasking, and difficulty summoning the right word in conversation.

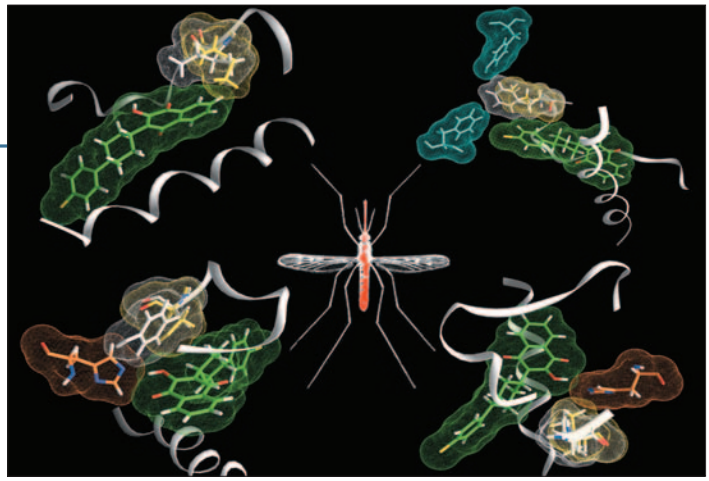
Persist: "For some people these are acute side effects of the treatment, and for some people these side effects actually persist long after the treatment," says Tim Ahles, Ph.D. The director of DMS's Center for Psycho-Oncology Research, Ahles studies the effects of chemotherapy on long-term cognitive function. "We are very interested in why some people have these long-term cognitive defects," he says. He and his collaborators want to know what factors make some patients more vulnerable to these effects than others.

Currently, the researchers are assessing the cognitive function of patients with lymphoma and breast cancer, both pretreatment and posttreatment. They are then evaluating associations between the development of long-term cognitive defects and several other variables. The variables they are looking at include the types and doses of chemotherapy the patients have received and the genetic differences among the individuals. For example, are patients who receive a particular regimen of chemotherapy more likely to develop long-term cognitive defects? Or is there a particular gene that triggers vulnerability to these side effects?

One particular gene the group is examining is called APOE. One version, or allele, of this gene, E4, has been associated with Alzheimer's disease and traumatic brain injury. Recent research by Ahles's team suggests that the carriers of APOE's E4 allele may have a higher risk of developing long-term cognitive defects after receiving chemotherapy.

Side effects: Most patients who experience chemo-related cognitive defects find that they return to normal shortly after they finish their regimen, but "for some people these side effects actually persist long after the treatment," explains Ahles. His group has published data showing that lymphoma and breast cancer survivors who received chemotherapy experience more cognitive defects five years after the conclusion of their treatment than do similar patients who received only nonsystemic treatment, such as surgery or local radiation.

Chemotherapy confers an increased chance of survival, of course, as well as an increased risk of cognitive defects. But these problems do affect long-term quality of life for some patients. Could it one day be possible to get the benefit without the risk? Ahles and his colleagues hope so. Their ultimate goal is not just measuring the problem but mitigating it. "If we really understood the mechanism," he says, "there will hopefully be drug interventions that may either prevent or reduce the negative cognitive impact of chemotherapy." KRISTEN GARNER



This graphic shows a mosquito, the vector for malaria, surrounded by molecular models of the antimalarial atovaquone as it loses potency against resistant strains.

Researchers take a swat at malaria

When battling any kind of resistance—even drug resistance—it pays to know thy enemy. In the case of the antimalaria drug atovaquone, DMS researchers recently confirmed the identity of "the enemy"—five specific mutations in an enzyme of the parasite that causes malaria. With this new understanding, the team hopes "to develop a drug that malaria cannot become resistant to," says biochemist Bernard Trumpower, Ph.D. "Malaria has become resistant to every drug that has been targeted to it."

Complex: Trumpower, who heads the lab that made the discovery, has spent years studying the cytochrome bc1 complex—the enzyme on which atovaquone acts—but only lately has he looked at its tie to malaria. About five years ago, a University of Michigan researcher phoned Trumpower to ask for his help studying atovaquone resistance in *Pneumocystis pneumonia*, once a major cause of death in AIDS patients. Soon Trumpower and his team learned that similar problems of resistance plagued the drug's effectiveness against malaria, too.

"In the case of *Pneumocystis* and malaria, there was evidence indicating that the resistance was due to mutations in the gene which codes for one of the proteins in this enzyme," Trumpower says. "That evidence was genetic coincidence." In other words, they'd found particular mutations in resistant *Pneumocystis* and in resistant malaria parasites. Trumpower's lab modeled each of these mutations in yeast and then tested their resistance. The enzyme without the mutations was sensitive to the drug, while the enzyme with the mutations was resistant. "So we biochemically confirmed, or proved, what was suspected from genetic, coincidental, guilt by association," he says.

Atovaquone is a "relatively difficult compound to chemically synthesize," notes Trumpower. As a result, the drug (which goes by the brand name Malarone) is expensive and thus is taken mostly by Westerners who travel to regions where malaria is prevalent. Trumpower, however, believes a drug his team is developing, with the help of Dartmouth chemistry professor Gordon Gribble, Ph.D., will be easier to synthesize, cheaper, and better. "If we are going to succeed, we will know in a three- to five-year period," he adds. JENNIFER DURGIN