Hope in Alzheimer's fight emerges from unexpected places

In drug development, sometimes you find what you're not looking for. In July, at the annual meeting of the Alzheimer's Association, which took place in Chicago, researchers presented data about the serendipitous discovery of two drugs that might help prevent cognitive decline. One is a blue dye once administered to treat urinary tract infections, and the other is a compound once studied as an antihistamine in Russia.

Other drug candidates designed around a popular theory of Alzheimer's disease progression have recently faltered in clinical trials. So the new, unexpected findings add an interesting twist in the search to identify the cause of the disease. At the recent meeting in Chicago, Samuel Gandy, chairman of the Alzheimer's Association's medical and scientific advisory council, commented that the drug pipeline is "developing now on all fronts and moving in some unexpected directions."

Shortly after Gandy spoke, Claude Wischik from the University of Aberdeen, UK, presented results from a trial in which his team had given 321 individuals with Alzheimer's a formulation of the laboratory reagent methylthioninium chloride, also known as MTC or methylene blue. After six months, subjects taking this compound experienced a significant improvement in cognitive function as compared with those receiving a placebo. Over the course of a year, the dye slowed the progression of Alzheimer's by 81% as compared to placebo.

Perhaps more startling than the numbers is the way in which Wischik came upon MTC. Back in the mid-1980s, he began using electron microscopy to study a protein called tau, which can form tangles of fibers that build up in the brains of people with Alzheimer's. Wischik was stunned to see that a dye used for electron microscopy called alcian blue caused the tau filaments to dissolve. After a late-night literature search, Wischik learned that psychiatrists had used a related dye, MTC, for manic depression as well as urinary tract infections.

Nearly a decade later, he succeeded in developing an assay that showed MTC blocks tau-tau binding (*Proc. Natl. Acad. Sci. USA* **93**, 11213–11218; 1996). "Once we knew that, we had it all," says Wischik, who in 2002 co-founded TauRx Therapeutics in Singapore to develop MTC and other potential treatments for neurodegenerative diseases.

At the Chicago meeting, scientists heard about another potential anti-Alzheimer's agent with unorthodox origins, called Dimebon. Developed by Russian scientists during the Cold War for undisclosed purposes, Dimebon eventually showed some antihistamine properties.

In further studies, Dimebon proved able to weakly inhibit an enzyme called acetylcholinesterase and to block the brain's *N*-methyl-D-aspartate (NMDA) receptors. That dual property seemed to combine in one substance the action of drugs now most frequently prescribed for patients with Alzheimer's.

The San Francisco–based biotech company Medivation acquired the patent for using Dimebon against Alzheimer's and sponsored a trial in Russia involving 183 subjects with mild to moderate Alzheimer's. Subjects receiving Dimebon performed significantly better on cognitive and behavioral tests compared with those given placebo. Over the course of a year, less than 20% of subjects on Dimebon worsened, compared with nearly 40% of placebo subjects.

Researchers speculate that Dimebon might save neurons by protecting their energy-producing machinery from dysfunction due to oxidative stress. "With most drugs, people spend years on the mechanism before it ever enters a human trial," says neurologist Rachelle Doody, at the Baylor College of Medicine, Houston, who was lead investigator in the Dimebon clinical studies. "Dimebon is unusual and interesting."

Puzzling proteins

These unexpected findings represent a sidestep from what's known as the amyloid theory, which hinges on the premise that abnormal processing of a protein called amyloid precursor protein and accumulation of its byproduct, called beta-amyloid, causes Alzheimer's. Notably, drugs that target amyloid precursor protein processing and beta-amyloid are faltering in clinical trials. For example, at the Chicago meeting, researchers from the Boston University School of Medicine presented disappointing results from the largest phase 3 trial targeting amyloid proteins to treat Alzheimer's disease. The drug, Flurizan, inhibits the buildup of toxic beta-amyloid. In an 18-month study of more than 1,600 individuals with mild Alzheimer's, Flurizan did not work any better than the placebo in any measure of efficacy.

At the same time, Elan-Wyeth's drug bapineuzumab showed lackluster results in an 18-month phase 2 trial of 234 subjects. Bapineuzumab is a monoclonal antibody that specifically targets beta-amyloid. Overall, subjects given the drug did now show improvement over placebo. It was only when the researchers broke down the subjects into a subset, roughly a third who did not carry an ApoE4 mutation (that increases risk of Alzheimer's), that an effect on cognitive and functional measures emerged.

The results are sobering but have not deterred researchers who have long held that beta-amyloid is the best target for an ultimate Alzheimer's therapy.

"I have not seen any waning of interest in amyloid hypothesis," says Maria Carrillo, director of medical and scientific Affairs for the Alzheimer's Association in Chicago.

"Scientists who are very knee-deep in these results understand that the failures of the drugs could really be based on so many other factors that are not related to amyloid itself." It could be, for example, that agents such as Flurizan never passed through the formidable blood-brain barrier, as they should.

As amyloid enthusiasts try to sort it out, however, a void has opened that leaves opportunity for chance. "Even though what we are doing is not the mainstream thing today," says Wischik, "you can't walk away from our data."

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Cautious outlook: Promising drugs have faltered