UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers develop new strategy for broad spectrum anti-viral drugs

DALLAS – Nov. 23, 2008 – Bavituximab, an anti-viral drug developed by UT Southwestern Medical Center researchers, shows promise as a new strategy to fight viral diseases, including potential bioterrorism agents.

In a study appearing in the December issue of *Nature Medicine*, groups of guinea pigs infected with a virus similar to Lassa fever virus recovered from the fatal disease when treated with bavituximab alone or in combination with a common anti-viral medication. Bavituximab treatment also cured mice infected with cytomegalovirus, an opportunistic infection that afflicts transplant and AIDS patients.

Dr. Philip Thorpe, professor of pharmacology at UT Southwestern and senior author of the study, proposed that phosphatidylserine, a lipid molecule that is normally positioned on the internal surface of a cell, flips to the outside of the cell when the cell is infected by a virus. His laboratory developed bavituximab, which binds to phosphatidylserine on the infected cells. Dr. Thorpe predicted that this interaction would muster the body's immune cells to attack and destroy the infected cells before the virus has a chance to replicate.

"When injected into the bloodstream, bavituximab circulates in the body until it finds these inside-out lipids and then binds to them," said Dr. Thorpe. "In the case of virus infection, the binding raises a red flag to the body's immune system, forcing the deployment of defensive white blood cells to attack the infected cells."

In the study, half of the guinea pigs infected with a virus similar to the Lassa fever virus were cured when bavituximab was administered alone. This is the first report of a therapeutic treatment being effective against advanced Lassa-like fever infections in animals. Lassa fever is an endemic disease in portions of West Africa, where the Lassa virus is carried by rats. As a hemorrhagic fever virus, Lassa is listed as a Category A bioterrorism agent – the same class as the Ebola and Marburg viruses – by the Centers for Disease Control and Prevention.

In a second experiment, researchers administered both bavituximab and the anti-viral

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medication ribavirin. Ribavirin works by a different mechanism than bavituximab; it stops virus replication in the cell. With this combination therapy, 63 percent of guinea pigs survived.

Dr. Melina Soares, instructor of pharmacology at UT Southwestern and lead author of the *Nature Medicine* study, said, "As viruses mutate, they become more resistant to existing anti-viral drug therapies. Using bavituximab to attack a lipid target could prove to be a new and effective strategy for treating virus infections."

Dr. Thorpe said that because phosphatidylserine on virus-infected cells is host-derived and independent of the virus, drug-resistance should be less problematic.

"This approach reduces the ability of the virus to escape attack by a drug," he said. "Viruses often dodge drugs by mutating into a different form that the drug is ineffective against. Host cells are a more immutable target."

Bavituximab is currently in clinical trials to treat patients with hepatitis C. The trials have shown that treatment is safe for patients, and researchers are reporting a reduction in their blood-virus load.

UT Southwestern researchers have found that phosphatidylserine flipping occurs in cells infected with influenza, the herpes simplex virus and viruses in the families of the small pox and rabies viruses. Other researchers have shown that this also occurs in HIV.

"It could very well be that this is a generic feature of enveloped viruses," Dr. Soares said. "It could lead to a new, broad spectrum anti-viral treatment."

Peregrine Pharmaceuticals has exclusively licensed bavituximab from UT Southwestern and has a sponsored research agreement to develop the drug further. Dr. Thorpe is a consultant to and has an equity interest in the company.

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