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Anti-Cancer Drug, Gleevec, May Be Effective Against Smallpox

The hallmark anti-cancer drug Gleevec may be effective in controlling smallpox infections or treating the complications caused by smallpox vaccinations, according to research at Emory University. Gleevec has been highly successful in treating chronic myelogenous leukemia in humans and has few adverse side effects.

Scientists administered Gleevec to mice and infected them with lethal doses of vaccinia virus, the poxvirus used to vaccinate against smallpox. They found that the drug reduced dissemination of the virus and the mice survived. Vaccinia is similar to variola, the poxvirus responsible for smallpox infection.

The findings were published online in the journal *Nature Medicine* on June 26.

The research was carried out by graduate student Patrick M. Reeves and colleagues under the direction of Daniel Kalman, PhD, assistant professor of pathology and laboratory medicine at Emory University School of Medicine.

The World Health Organization declared smallpox eradicated in 1980, and routine vaccinations ceased in 1972. However, a large portion of the population is considered extremely susceptible to smallpox infection, and bioterrorism experts are still concerned about a deliberate outbreak. Complicating matters, vaccination is known to cause serious side effects in immunocompromised individuals or those with certain skin diseases. Variola infections or serious adverse reactions to vaccination are treated with vaccinia immune globulin (VIG) and the drug cidofovir. VIG is only partially effective, however, and cidofovir is extremely toxic.

The Emory scientists decided to test Gleevec against poxviruses following their discoveries about how the viruses interact with their host cells on a molecular level. After poxviruses enter a mammalian cell, the virus particles, or virions, reproduce in the cell's cytoplasm outside the nucleus, become encased in an envelope that helps them evade the immune system, and then travel outward to the surface of the cell. There, some of the virions fuse with the cell's plasma membrane. Reeves, Kalman and colleagues found that these enveloped viruses hijack host-cell proteins called "Abl tyrosine kinases," which allow the

virions to detach from the cell and spread to other cells. Gleevec's cancer-fighting power comes from its ability to block the same Abl tyrosine kinase, which become mutated in chronic myelogenous leukemia.

The Emory scientists speculated that Gleevec might be effective in controlling poxvirus pathogenesis without eliciting drug resistance. "Because we are inhibiting the host cell molecule and not a viral molecule, the likelihood of developing resistance to this drug treatment is minimal," explains Dr. Kalman. "It would be very difficult for the virus to overcome the blockade of a host cell factor, because it would have to completely change its virulence program. Think of a virus as a car driving down a road. Conventional anti-viral drugs might cause the car to have a flat, which is easily replaced with a puncture-proof tire ? that's resistance. But, Gleevec is like an avalanche across the road. The car would have to learn to fly to get past it."

Dr. Kalman and his colleagues also are studying the effects of anti-cancer drugs on pathogenic E.coli, and he believes the concept of using anti-cancer drugs to treat microbial infections may prove to be more generally applicable. "Many pathogens use host molecules, particularly host signaling molecules, as part of their pathogenic program," he says.

The research was supported by grants from the National Institute of Allergy and Infectious Diseases, a part of the National Institutes of Health; the Southeastern Regional Center for Excellence in Bioterrorism (SERCEB); Emory University; and Emtech Biotechnology Foundation.

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