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Prodrug could help curb skin toxicity related to EGFR-inhibiting cancer drugs

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There may be a way around the harsh skin toxicity associated with a widely used cancer drug, according to a study published online this week in *Cancer Biology and Therapy* by researchers from City of Hope and the Kimmel Cancer at Jefferson.

Cetuximab (Erbitux) is a monoclonal antibody that binds to and inhibits the epidermal growth factor receptor (EGFR). It is widely used to treat colorectal cancer and head and neck cancer. Although cetuximab and other EGFR inhibitors are associated with a lower rate of side effects compared with conventional chemotherapy, adverse effects of the drugs often include a dose-limiting skin rash and gastrointestinal symptoms.

Adverse events in antibody therapy are frequently due to the binding of antibodies to normal tissue in addition to tumor tissue, according to Ulrich Rodeck, M.D., Ph.D., professor of Dermatology and Cutaneous Biology at Jefferson Medical College of Thomas Jefferson University. By "masking" the antibodies so they preferentially bind to the tumor tissue, the toxicity may be reduced or avoided.

"We've designed a prodrug in which the antibody is masked by an engineered form of the antigen, preventing it from binding to antigen on normal tissue," Dr. Rodeck said. "However, when the antibody reaches the tumor tissue, enzymes prevalent at tumor sites cleave the mask off, and the antibody can now engage the antigen at the tumor site."

The prodrug contains the antigen binding sites of two different EGFR-

specific antibodies: 425 (matuzumab) and C225 (cetuximab). Each antibody is connected via peptide linker to the antigen recognized by the opposite antibody. The linkers contain sites susceptible to proteolytic cleavage by metalloprotease 9 (MMP-9), an enzyme that is frequently overexpressed in epithelial malignancies. Cleavage of the complex leads the antibodies to become "unmasked" and able to bind to the antigens on the tumor cells.

"This work provides proof-of-principle evidence that the concept is feasible, and sets the stage for future studies using tumors grown in vivo," Dr. Rodeck said.

The print version of the study will be published in the November 15 issue of Cancer *Biology and Therapy*.

Source: Thomas Jefferson University (news : web)