The First FDA-Approved Antibody-Drug Conjugate

**Significance**: The enediyne-containing antitumor antibiotic calicheamicin induces double-stranded DNA breakage and is highly cell-toxic. Conjugation of calicheamicin to a humanized monoclonal antibody against CD33, an adhesion protein that is expressed on the cell surface of leucoblasts, allows its targeted delivery to the non-solid tumor acute myeloid lymphoma (AML). This construct was the first FDA-approved antibody-drug conjugate (ADC) and was marketed as Mylotarg. It was retracted in 2010; however, calicheamicin ADCs have now been re-evaluated as therapeutic.

**Comment**: N-Ac-γ was linked via a hydrazone to lysine residues on a humanized monoclonal antibody against the tumor antigen CD33 and succumbs to hydrolytic hydrazone cleavage upon endocytosis. The conjugation of calicheamicin to an antibody was previously reported (Cancer Res. 1993, 53, 3336) and, here, the authors investigate different linkers to produce a more potent and selective agent.