Quantitative systems pharmacology model of a masked, tumor-activated antibody

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therapeutic monoclonal antibodies bind proteins on tumors, which can enable the killing of cancer cells. However, there can be collateral damage to healthy tissues that also express those proteins. At CytomX, researchers are exploring the use of a new class of antibodies called Probody™ therapeutics. Masks attached to the ends of a Probody therapeutic can “blindfold” the antibody and reduce its binding to healthy tissues. However, when the antibody encounters a tumor, proteases—enzymes in the tumor microenvironment—can remove these masks to activate the antibody. In this way, Probody therapeutics are designed to maximize anti-cancer activity while minimizing harm to healthy tissue.

In a new study, researchers used computer modeling to predict how Probody therapeutics can be tuned to achieve this effect. This model, comprising thousands of equations, estimates the amount of both masked and unmasked (or activated) forms of the antibody in the tumor and in the rest of the body after dosing. This enables researchers to explore how changing Probody therapeutic properties affects their biodistribution.

One example is CD166, a new protein target for Probody therapeutics whose broad and high expression in both tumors and healthy tissues precludes the development of a traditional antibody therapeutic. The model was informed using data obtained in monkeys administered Probody therapeutics targeting CD166 with increasing mask strengths. The model was then used to predict what would happen in human cancer patients. The model predicted that stronger masking would result in less Probody elimination via target binding, which would lead to increased levels of circulating Probody therapeutics and more antibody available to enter tumor cells. The model also suggested that the strength of the mask would influence the level of CD166-mediated uptake in healthy tissue compared to that in tumors.

Model projections also indicated that Probody therapeutics would circulate largely in the...
masked rather than the activated form, which is important to avoid binding to healthy tissue. The model projected that the activated form would be eliminated following binding to target in the tumor before appreciable amounts would leak back into the circulation. This finding is consistent with experimental observations in both animals and human patients.

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