Chemical & Engineering News

Latest News

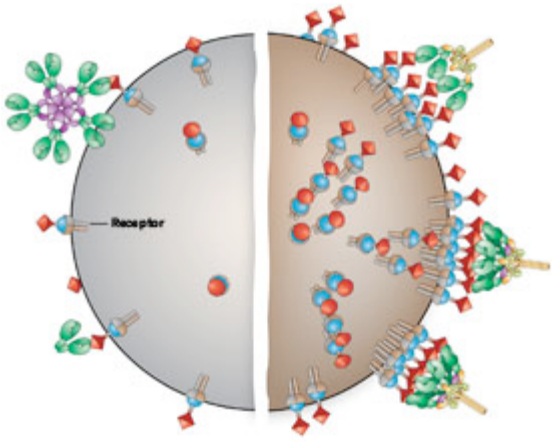
February 14, 2007
Also appeared in print February 19, 2007, p. 10

Chemical Biology

Strength In Numbers

Low-affinity, multivalent interactions recruit antibodies to kill cancer cells

Celia Henry Arnaud



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TARGETING CANCER Bifunctional molecules (red and blue) target membrane receptors and recruit antibodies (green and purple) that kill cells with high levels of receptors. Cancer cells (right) have more of the receptors than normal cells (left).

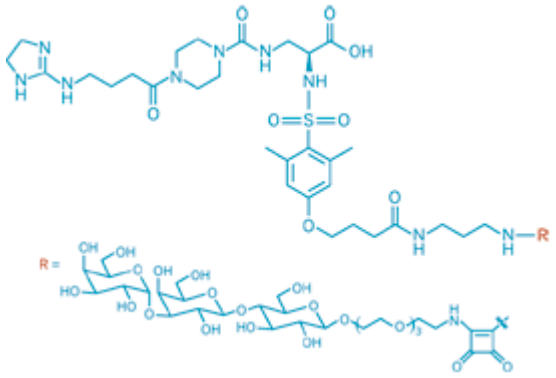
Low-affinity, multivalent interactions can be more effective at killing cancer cells than high-affinity interactions, according to research by biochemistry professor Laura L. Kiessling, postdoc Coby B. Carlson, and coworkers at the University of Wisconsin, Madison.

Nature uses a multitude of weaker interactions to distinguish one cell from another, Kiessling says. That way, if an agent interacts with the wrong type of cell initially, it easily can be displaced or dissociated. In contrast, most pharmaceutical targeting is based on a single high-affinity interaction.

Kiessling and her coworkers target cancer cells with a small bifunctional molecule (*ACS Chem. Biol.*, DOI: 10.1021/cb6003788). One part of the molecule is a peptide mimic that binds tightly to cell-surface receptors known as $\alpha_v\beta_3$ integrins. The peptide mimic is attached to a carbohydrate called the α-Gal epitope. Human anti-Gal antibodies bind weakly to individual α-Gal epitopes but bind tightly when many are displayed together on the cell surface. "The integrin will be targeted with a high-affinity interaction, but the toxic agent is only recruited when you have the multivalent interaction," Kiessling says. Her group reported the synthesis of the molecule previously (*ChemBioChem* **2007,** *8,* 68).

The researchers target the integrins because they are involved in the formation of new blood vessels. Integrins can be more abundant on cancer cells, and they are prevalent on the new blood

vessels that tumors induce. "You don't need a receptor that's found solely on tumor cells," Kiessling says. "You just need one that's found in a significantly higher proportion" on tumor cells than on normal cells.



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Ligands consisting of a peptide mimic (top) and α-Gal (bottom) target integrin receptors.

With the α-Gal-peptide combination, antibodies are recruited only to cells with high levels of integrins on the surface. If the α-Gal is replaced with the anticancer drug doxorubicin, the combination kills even normal cells, which generally have low levels of integrin on the surface compared with cancer cells. Thus, the doxorubicin conjugate is less selective for the cancer cells.

The work is a "clever use of an inherent immune mechanism to exploit the fact that there are molecules that are more densely expressed on the surfaces of tumor cells than in normal tissues," says Erkki Ruoslahti, a cancer researcher at the Burnham Institute for Medical Research, in La Jolla, Calif. "Data from in vivo animal models would be needed to determine whether this approach has potential for diagnostic or therapeutic use in cancer patients."

Kiessling is working with Paul Sondel, an oncologist and geneticist at UW Madison, to do in vivo studies to determine whether the strategy will work in animals. In addition, Kiessling is interested in using ligands that target two different cell-surface receptors to increase the selectivity for disease cells even more.

Chemical & Engineering News
ISSN 0009-2347