# Selective integrin ligand may facilitate specifically attacking cancer cells

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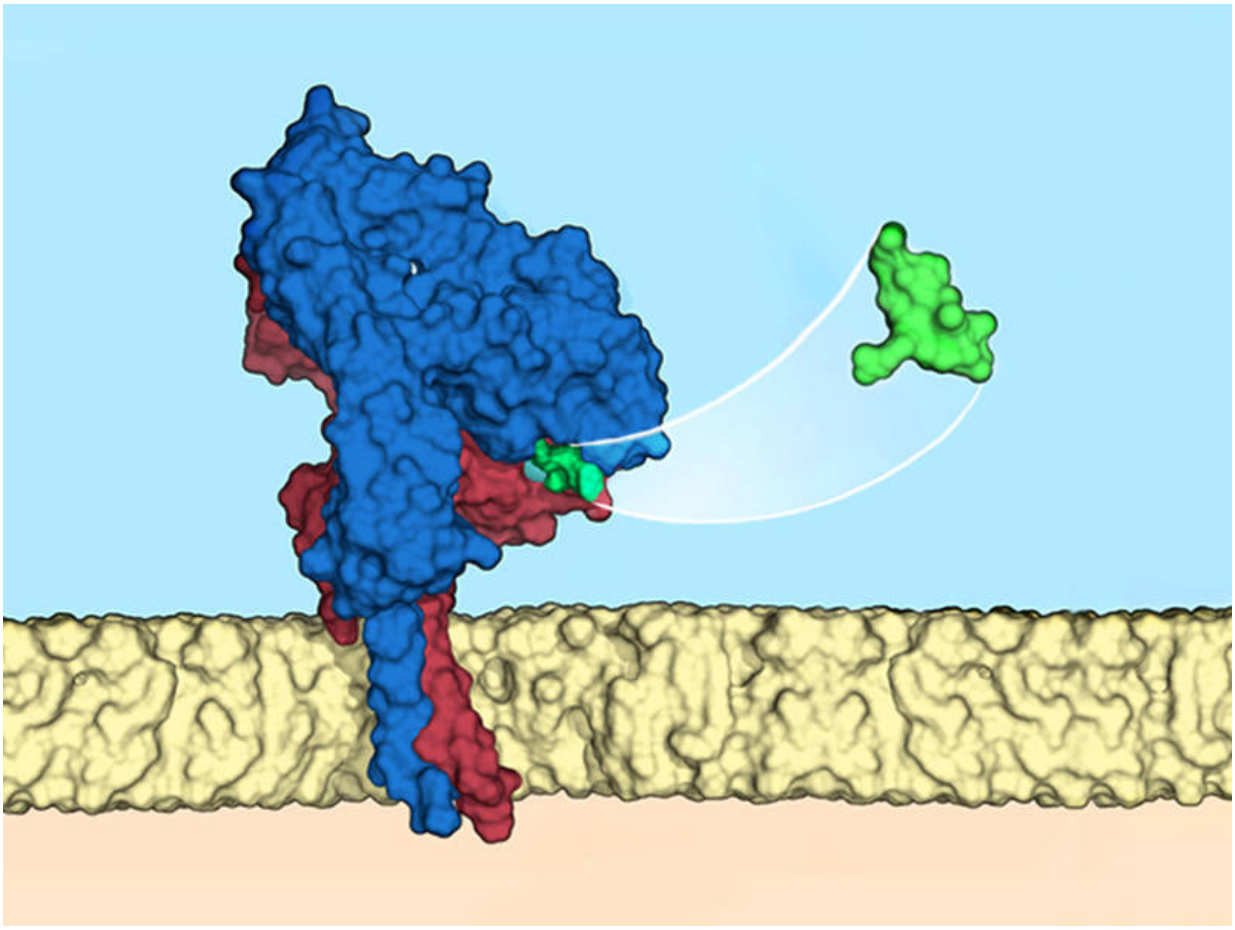

The ligand (green) fits like a key to a specific integrin (blue/red) on the surface of the tumor's cell membrane (beige). One of the ligand's amino acids, a lysine, can be used to attach diagnostic or anti tumor substances. Credit: Francesco S. di Leva, Luciana Marinelli / Università di Napoli Federico II

Integrins help cells communicate with and adapt to their environment. Also cancer cells depend on their properties to survive and spread throughout the body. Now scientists at the Technical University of Munich (TUM) have successfully developed a small, highly active molecule that binds to a specific integrin that operates in many types of cancer. In the future it may allow patient-specific diagnoses and subsequent targeted treatment of tumor cells.

Integrins are among the most important links between a cell and its outside world. They are found on the surface of cells and anchor them to other cells or substances in the space between cells, the so-called 'extracellular matrix.' This direct contact not only holds cells within their groups, it also allows them to receive signals from the environment and react to them—for example, by growing, dividing or leaving a group.

When a special protein in the extracellular matrix, a so-called ligand, bonds to integrin, various signal cascades are initiated inside the cell. Without integrins cells would be 'blind', 'deaf' and 'dumb'—and, as such, hardly able to survive.

## The aim: characterizing cancer cells

But, cancer cells deploy integrins for their very own purposes. They use them to break loose from tumor tissue, penetrate blood vessels and ultimately lodge themselves into other tissue as metastases in the lungs or bones, for example. However, precisely which of the many integrin subtypes is at work is very individual and can vary from patient to patient.

"If we knew which integrin subtypes are active in the specific cancer of a given patient, we could attack these using appropriate active agents," explains Tobias Kapp, doctoral candidate in Professor Horst Kessler's workgroup at the TUM Institute for Advanced Study and the TUM

Department of Chemistry. "For this we need compounds that attach to a single integrin as specifically as possible."

Now Kessler, Kapp and his colleague Dr. Oleg Maltsev have successfully developed just such a ligand: A ring-shaped compound, which attaches to the alphaVbeta6 integrin, that appears in many different kinds of cancer and also plays a large role in fibroses.

## A promising active agent

The new molecule fulfills many requirements of a potential medical agent. It selectively docks only to the alphaVbeta6 integrin—an important prerequisite for the future deployment as a medication with only minimal side effects.

In addition, it attaches to most of the alphaVbeta6 integrins even at relatively low concentrations, making it effective even in small doses. It is also durable due to its cyclical structure and, in contrast to integrin ligands found in nature, breaks down only slowly in blood plasma.

The new ligand has one more important characteristic in store: One of its amino acids, a lysine, can be used as a 'hitch' for docking other substances to the compound. "This is of great significance if you want to use the ligands as a diagnostic tool," explains Kapp. "For example, you can then dock substances that can be made visible using medical imaging equipment."

In this way tumors can be characterized and then fought using very specifically targeted therapies. If successful, this would represent a great advance in contrast with conventional cancer therapies, which are usually very broadly applied and thus also damage healthy cells.

# Step by step to the optimal binding partner

The scientists used a protein of the foot-and-mouth disease virus as a template for the ligand. This natural alphaVbeta6 ligand uses an alpha-helical structure to bind to the integrin. The researchers reconstructed the helix using a small ring structure comprising nine amino acids.

Using a multi-stage selection process they tested numerous variants until the most suitable molecule was identified. To this end, they also used a proprietarily developed new technology in which the side chain of the amino acid arginine is used as a kind of molecular switch. This influences which integrin subtype the ligand attaches to selectively.

"We now know the form of the lock and we know how to make the matching key," says Professor Kessler. "This opens the door to a personalized medicine with which we can take patient-specific action against tumor cells."

**More information:** O. V. Maltsev, U. K. Marelli, T. G. Kapp, F. Saverior Di Leva, S. Di Maro, M. Nieberler, U. Reunig, M. Schwaiger, E. Novellino, L. Marinelli, H. Kessler, Stable Peptides Instead of Stapled Peptides: Highly Potent αvβ6- Selective Integrin Ligands, *Angewandte Chemie*, DOI: 10.1002/anie.201508709

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