Mysterious molecular phenomenon could boost precision of targeted drug delivery

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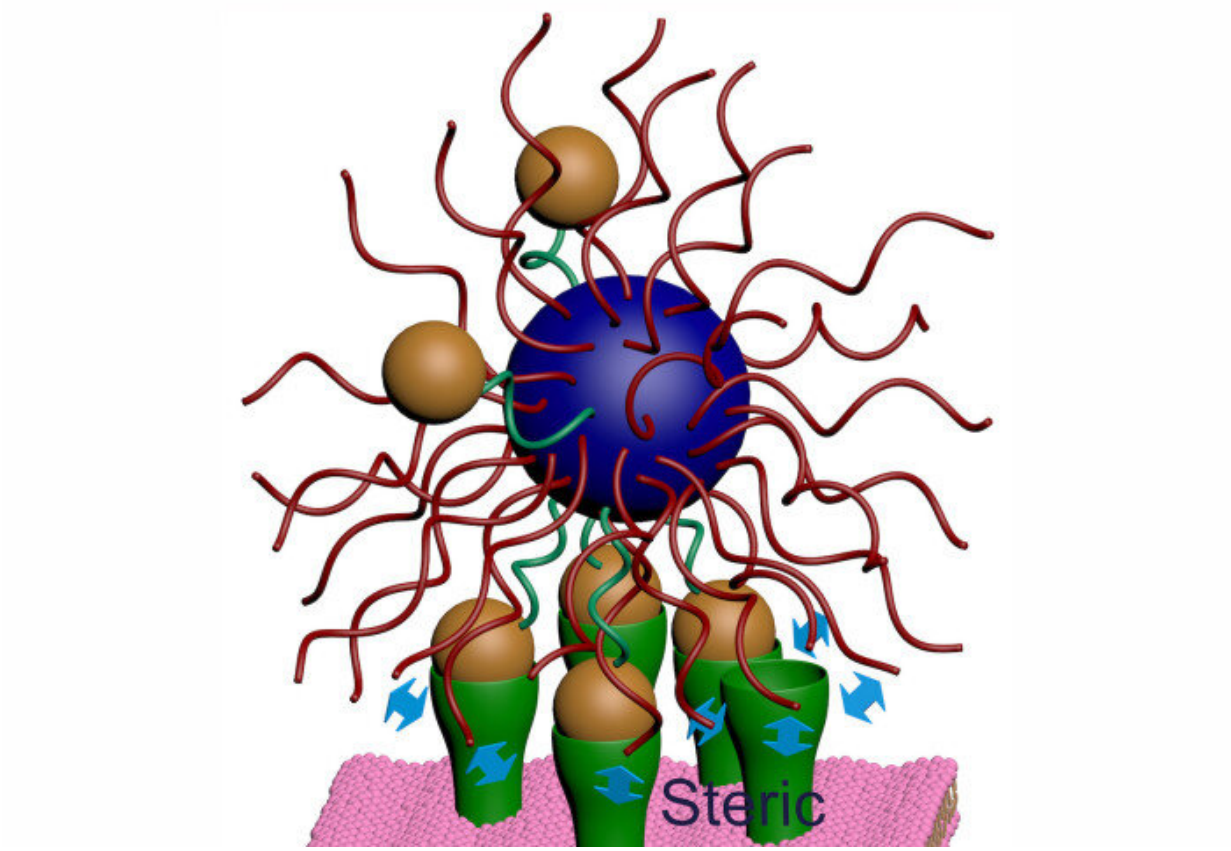

Nanoparticle (blue) coated with ligands (orange) interacting with a receptor (green)-coated surface. Credit: Imperial College London

A growing area of medicine looks at how cellular binding observed in nature—where molecules like viruses or proteins bind to specific

receptors on a cell—can be mimicked to aid drug delivery.

Those developing targeted drug therapies aim to recreate this precise binding to develop nano-sized drug carriers that attach only to diseased cells. Once attached, these carriers would release their therapeutic load without affecting healthy cells. If drugs can be specifically targeted in this way, treatments would cause far fewer side effects.

One way to identify which cells are diseased is the number of receptors they express. Cancer cells, for example, tend to express more certain types of receptor than healthy cells.

Now, in a multi-center collaboration led by Imperial and UCL, involving Beijing University of Chemical Technology, the Institute of Physics in Beijing and the Institute for Bioengineering of Catalonia, researchers have demonstrated how a mysterious molecular concept that the authors dubbed 'range selectivity' could be used to target diseased cells with high specificity. Range selectivity, until now a mysterious phenomenon, is where molecules called ligands attach only to cells whose receptors reach a certain number.

Senior author and principal investigator Dr. Stefano Angioletti-Uberti, of Imperial's Department of Materials, said: "I came across the concept of range selectivity completely by accident. During my theoretical investigation of receptor-ligand binding I noticed that ligands weren't attaching above a certain threshold of receptor density and had my team re-check our code before realizing it wasn't a bug."

In nature, range selectivity happens because of a balance of attractive and repulsive forces at the molecular level. Past a certain threshold the repulsive force must outweigh the attractive, and so binding is far less likely to take place. This is due to certain physical properties of ligand-receptor interactions.

Following their realization, the group at Imperial used statistical mechanical modeling to show how modifying certain parameters could tune the balance of attractive and repulsive forces. This provided a 'molecular handle' to tune the upper and lower limit of the selectivity range. Their colleagues at UCL, led by Professor Giuseppe Battaglia, then confirmed these theoretical predictions using experimental data.

Researchers tune the force balance using a 'molecular handle'

Dr. Angioletti-Uberti added: "The key to unlocking highly targeted drug therapies could lie in directing drug carriers towards cells with a precise number of receptors.

"If we can find out which receptor densities are specific to different diseases and apply what we've demonstrated to drug carriers, we could treat those diseases effectively with fewer side effects."

Alongside drug targeting, the researchers say their work offers an important insight that could change the way future studies in this field are conducted. For example, researchers could now take into account that simply increasing the number of receptors does not necessarily increase the probability of binding, and in fact may cause it to significantly decrease.

It also offers clues that could go some way to explain why tumors evade attack from the immune system.

Dr. Angioletti-Uberti said: "Could it be that tumor cells' receptor densities fall outside the range toward which immune cells are programmed to target?"

The authors are now looking into how to optimize receptor density on cells to ensure maximum binding, as many parameters like receptor and ligand type can affect the strength of these bonds.

Dr. Angioletti-Uberti added: "Nature might already be using this form of binding to its own advantage, or indeed our disadvantage. Understanding this fully could lead to a wealth of disease-targeting possibilities."

More information: Meng Liu et al. Combinatorial entropy behaviour leads to range selective binding in ligand-receptor interactions, *Nature Communications* (2020). DOI: 10.1038/s41467-020-18603-5

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