Nanotech strategy speeds up hunt for 'smart drugs'

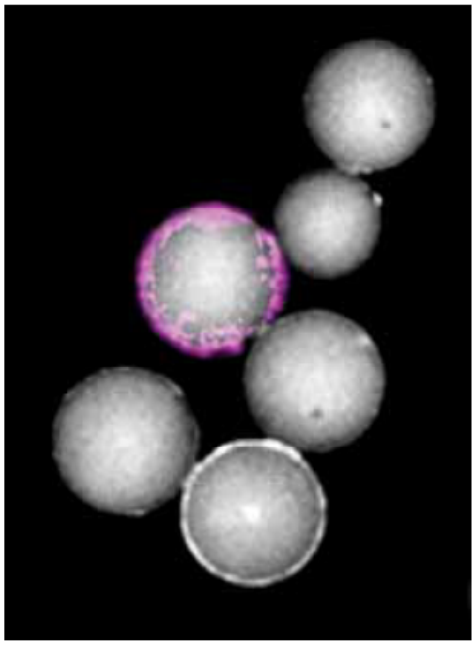
Canadian researchers have developed a new nanotechnology-based method to screen for peptide sequences that bind to cancer-specific targets. Such sequences could lead to improved 'smart drugs' that attack cancer cells while leaving normal ones alone.

Many smart drug candidates use monoclonal antibodies from mice as their targeting agent. One example is trastuzumab, also known as herceptin: an antibody that interferes with the HER2/neu receptor that is overexpressed in breast cancer cells. However, antibodies are large proteins which can be difficult to attach to drug-carrying nanoparticles; moreover, the body can raise its own antibodies against them. In contrast, short peptide sequences only a few amino acids long are easier to synthesize and attach to nanoparticles. By incorporating right-handed D-amino acids which are not found in nature, these sequences can be protected from the body's own defence systems.

Currently, peptide sequences that target cancer can be identified by coating 90 µm polymer beads with random sequences of peptides: for a sequence eight amino acids long there are billions of possible combinations. These are then mixed with the cancer-specific protein of interest attached to a fluorescent antibody. The ones that bind are identified by the fluorescence and extracted manually. "This is frustrating and takes a lot of time," says John Lewis, a cancer researcher at the University of Alberta. "As well, because the antibody is always attached to the same part of your protein, you're biasing the way it's displayed."

Lewis teamed up with Len Luyt, a chemist and oncologist at Western University, to create a new method. Instead of labelling the protein of interest with a fluorescent antibody, the team coated it onto smaller beads (two µm in diameter) which are both magnetic and fluorescent. This "bead-on-bead" approach presents multiple faces of the protein to the potential binding sequences, leading to a less biased test. The bound particles can then be extracted with a magnet, which is a lot easier than separating them manually. "You can complete the entire process from beginning to end in about 10 days," says Lewis. The research is published in *Nano Letters*.

The team has validated the approach by finding novel peptide sequences that target $\alpha_V\beta_3$ integrin, a protein that's overexpressed on certain types of cancer cells. They're now working on attaching the sequences to therapeutic nanoparticles or imaging agents.



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Protein-coated fluorescent beads two µm in diameter stick to the surface of a larger bead (90 µm diameter) coated with short peptide sequences. This new 'bead-on-bead' approach provides a faster way to screen for peptide sequences that can target proteins which are overexpressed on cancer cells, enabling the development of 'smart drugs.'