Manmade antibodies hold biomedical promise (w/ Video)

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Antibodies are the immune system's warriors. Their role is to pinpoint disease pathogens, attaching to them and neutralizing their effects. Though antibodies are of great value for biomedical research, the process of creating them has been time-consuming and tedious. Researchers at the Biodesign Institute at Arizona State University have developed a much faster and simpler way of making synthetic antibodies, by carrying out the usual steps in reverse.

Stephen Albert Johnston and Chris Diehnelt of Biodesign's Center for Innovations in Medicine at Arizona State University, along with their colleagues, have developed a technique for constructing amino acid sequences, then linking them together to form a synthetic antibody, or synbody, that can bind with one or more protein molecules contained in the vast repository of human proteins—the proteome.

The group has developed a high affinity synbody capable of binding with AKT-1, a critical protein believed to play a role in aging, obesity, and cancer. In addition to the potential of synbodies to directly target proteins associated with disease-causing microbes, they also show great potential as a research tool and building block for novel diagnostics and treatments. The team's findings appear in the current issue of the journal PLoS ONE.

As Johnston notes, traditional antibodies are already in wide use for biological research, but the existing procedures for producing them are laborious and costly. "Traditional antibodies are made by taking the

protein you want to bind," Johnston says, "and injecting it into an animal, which responds by making antibodies." These antibodies, or the cells that produce them, are then extracted.

Rather than beginning with a protein in order to produce an antibody, the new technique involves building an antibody first. "We turn the whole process on its head, making the antibody chemically, then finding out what it's an antibody to," Johnston says.

To accomplish this, a 20-unit random sequence of amino acids are joined together like beads on a necklace to form a peptide. By uniting two of these peptide chains, linked together by means of a chemical scaffold, a binding molecule or ligand is created, which can attach to a specific protein with high affinity. The resulting synbody may then be screened against a multitude of human proteins, to find its mate.

The strategy relies on the fact that the binding affinity of two such amino acid sequences is the product of their combined affinity, allowing two peptides with weak attraction to a given protein to be joined to produce a synbody with strong binding properties. Remarkably, the assemblage of both the individual peptides and the synbody are carried out randomly.

The raw material for the synbody comes from a library of 10,000 peptides, with each amino acid sequence randomly composed. As Johnston explains, "the randomness turned out to be the key to all of this, because a random sequence has more flexibility and degrees of freedom than life sequences do." Each resulting linear peptide chain is able to find 2 or 3 points of contact with virtually any protein. When two such peptides are combined to form a synbody, a high-affinity ligand is produced, displaying specificity for a given protein.

Currently, the only limiting technological consideration is the number of

proteins that can be placed on an array slide and that capability, as Johnston notes, is rapidly improving. Another key advantage in the use of synbodies is that they remain stable over time, unlike their biological counterparts, making them far more suitable for diagnostic assays.

Exposing random synbodies to multiple proteins helps build a library of effective ligands over time. To create a synbody to a particular disease protein on the other hand, the protein is exposed to multiple peptides. Once two are identified that link to the protein, they may be combined into a disease-specific synbody—an effective, though much slower process.

The ability to produce ligands to all 30,000 proteins in the human proteome would be a boon to science, offering the ability to study any protein in the body with fine-grained specificity and to develop a suite of new diagnostic tools. Proposals exist to complete such a daunting task by traditional means, at an estimated cost of $1 billion over the course of ten years.

"I'm too impatient," Johnston says. "And it's too much money." The synbody approach, in which a Lego-like peptide kit is used to produce high-affinity ligands offers a plausible route to addressing the problem by high throughput means at substantially lower cost.

More information: http://dx.plos.org/10.1371/journal.pone.0010728

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