Peptibodies: the new cool technology

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Small peptides hold therapeutic promise but are degraded in the body within minutes. Antibodies are more stable but can take years to develop. Now Amgen (http://www.amgen.com) has created a hybrid of the two: the peptibody. Ken Wild unveiled the company's development of an analgesic peptibody targeted to nerve growth factor (NGF) at the Spring Pain conference, held in Grand Cayman, April 24–May 1 (http://www.caymanconferences.com/pain/pain_meeting_info.htm). The peptibody reduced thermal hyperalgesia and tactile allodynia – over-sensitized pain states – in rat models of neuropathic pain.

Stabilizing stem

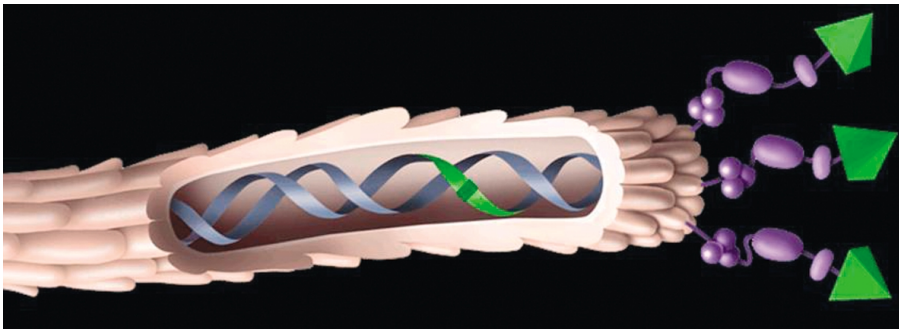
Within the antibody heavy chain is the Fc, or fragment crystallization protein, which makes up the 'stem' of its Y-shaped structure. Amgen has exploited Fc's stabilizing properties by coupling it to a short, 24-amino acid peptide that binds to NGF. They used the phage display technique to find the best peptide sequence that would bind NGF.

Wild describes the process as 'a cool technology'. Amgen began by setting the length of amino acids they were aiming for – around 20. A phage library then provided hundreds of millions of random sequence combinations. Each phage – a small bacterial virus consisting of protein-coated DNA – carries a gene for one of these peptides. Bacteria infected with the phage then duplicate the phage, each of which expresses a particular peptide on its surface. Phage libraries are commercially available from companies such as Dyax (http://www.dyax.com/).

Go fishing

Next, Amgen made NGF the 'bait'. 'Then you go fishing,' says Wild, for specific peptides that bind NGF-coated beads. They were able to improve the specificity with affinity maturation, by constraining certain amino acids of the sequence and repeating the process.

Says Wild, 'now you've got a peptide, great. How are you going to make a drug out of that?' Amgen is hoping that they can do it by coupling the unstable peptide to Fc. Unlike an antibody, which requires dimerization of two different gene products, Amgen found it possible to construct a gene that codes for Fc and for the new NGF-binding peptide. Also unlike antibodies, peptibodies can be mass produced by *Escherichia coli*, an advantage because 'growing [mammalian] CHO cells in giant vats is a bit more tricky than growing a vat of bacteria. In general, this whole process is cheaper and easier.' Once the peptibody is isolated, you're left with 'insoluble chunks' of protein. 'That's where the biotechnology really comes in,' says Wild. 'Through whatever tricks necessary, you refold it and get it into solution properly folded.' Bacterial proteins lack posttranslational modifications, which are apparently unnecessary for dimerization.



An artist's rendering of a phage, with inserted gene and the peptide it encodes displayed on its surface. Image courtesy of Dyax (http://www.dyax.com/).

A new class of drug for pain

Arnon Rosenthal, of Rinat (http://www.rinatneuro.com) has been developing a more traditional antibody NGF antagonist as a therapeutic. He points out several weaknesses of a peptibody drug, namely its still-short half-life and foreign nature. Wild estimates that the body would raise an immune response to a peptibody within about a week. These limitations would prevent its use against chronic pain, but Rosenthal says it could be used 'for acute, 'one-shot' applications, such as cancer applications, because the immune system is put down; or in conjunction with immunosuppressants.'

After all, he points out, 'Most of the pain medications available today have been used since World War I, when morphine was the most prevalent drug. Any new class of drugs for pain would be interesting and extremely useful.' Wild adds, 'Though its clinical use has not yet been proven, [the peptibody] clearly, as a platform, deserves exploration.'

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