The natural L-amino peptide has a relatively short half-life, whereas the D-peptide is safe from proteolysis. Kaumaya's challenge was to make a stable peptide while preserving the receptor structure. By creating a 'retro-inverso' molecule, in which the sequence is reversed and inverted, his laboratory made a stable peptide that is a perfect mirror image of the CD28 receptor's binding motif.

### A question of specificity

Before entering human trials, Whitacre says the strategy must pass a crucial test in animals: does it act as a global immunosuppressant? 'If a person [treated with the redesigned peptide] meets a virus, can they still fight it off? We don't want to lay people open to infection.'

Another piece of data from the study might hint at the answer: in mice, treatments with the peptide mimic reduced the T-cell population through apoptosis. 'Now we need to go in and ask, which specific T cells are they? Is it a global lowering of all T-cells?' says Whitacre. By contrast, if it is only pathogenic-specific T cells that are affected, then Whitacre says 'that's very exciting. Then we're purging an MS patient of the specific disease-causing T cells.'

Although this study is an early step toward the development of a treatment for MS, the data in the EAE mouse model even hint that the peptide might actually reverse the course of MS, according to Whitacre. Further, because it acts at the source of the immune attack, it could also work in other problems involving the immune system, such as graft vs host disease or organ transplantation.

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# Boost for retinoic acid cancer therapy

**Martina Habeck**, freelance writer

A naturally occurring protein can dramatically enhance the ability of retinoic acid (RA), a common cancer therapy, to inhibit the proliferation of breast cancer cells. The finding may make it possible to fine-tune this drug's activity to avoid harmful side effects.

RA, a vitamin A derivative, is a small signalling molecule that plays an important role the regulation of cell growth, differentiation and death. Because of their ability to drive cells towards apoptosis, RA and other retinoids are used successfully in the treatment of acute promyelocytic leukemia. They also have potential to prevent cancers of the skin, head and neck, and lung.

Although the function of RA in regulating cell growth and differentiation has been known for a while, the molecular mechanisms by which these functions are regulated are still under investigation. Scientists know that RA binds to a family of nuclear transcription factors, the RA receptors (RARs), thereby inducing the transcription of target genes. RA can also bind to two small proteins called cellular RA-binding protein (CRABP) I and II, but until recently, this was thought not to play a major role in the transcriptional activity of RA. Most people assumed that the function of the binding proteins was to keep RA, which is a lipophilic compound, in solution.

Noa Noy and her team at Cornell University (http://www.cornell.edu) were intrigued by the fact that the cell should use two proteins to perform this simple task. They therefore wanted to see what specific functions these binding proteins might have. In 1999, they reported that CRABPII, but not CRABPI, actually enhances the ability of RAR to upregulate its target genes [1], and earlier this year, they showed how this was achieved. Their studies revealed that the cytosolic CRABPII protein moves to the nucleus once bound to RA. There, it interacts with RAR, and this interaction augments the transcriptional activity of RAR (Fig. 1) [2].

'These results are undoubtedly exciting,' says Lucia Altucci of the Second University of Naples (http://www.unina2.it). 'The observation that CRABP-II enhances the transcriptional activity of RARs by directly 'channeling' the ligand to the receptor introduces a novel concept into the present schemes of ligand action.'

### Implications for treatment

Noy and colleagues then began to wonder whether the ability of CRABPII to enhance the transcriptional activity of RA will also result in increased therapeutic activity. They tested this hypothesis by

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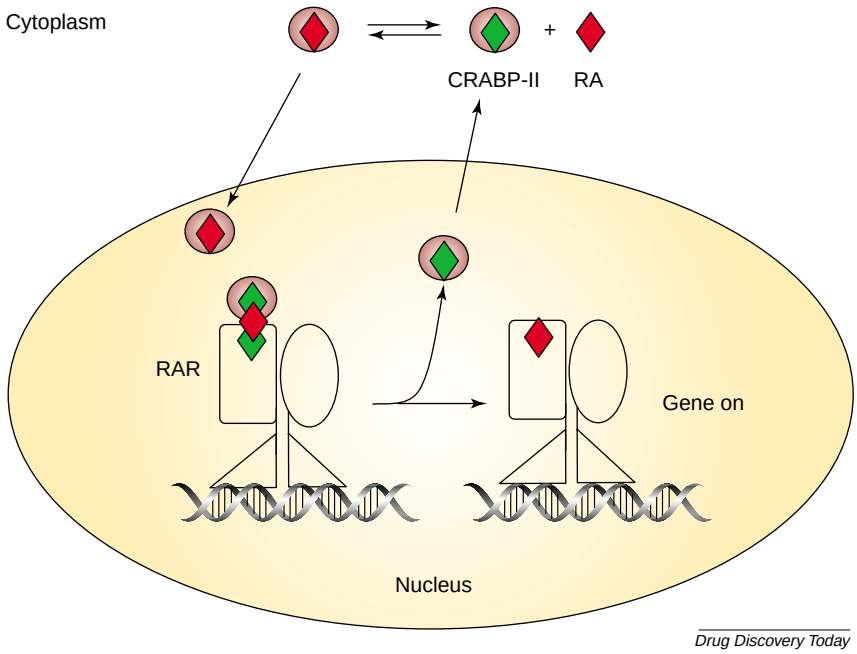


**Figure 1.** Mechanism of action of cellular RA-binding protein (CRABP-II). Upon binding of retinoic acid (RA) in the cytoplasm, CRABP-II moves to the nucleus where it 'channels' the ligand to RAR. RAR is thus rapidly activated even at very low RA concentrations. In turn, activation of RAR results in the upregulation of multiple target genes. Figure kindly provided by Noa Noy; adapted from ref. [2].

expressing CRABPII in cultured breast cancer cells and found that they become much more sensitive to RA [2]. According to Noy, 'there are two or three orders of magnitude difference in the ability of RA to kill these cells.'

To confirm their results *in vivo*, Noy and colleagues tested the effect of CRABPII in transgenic mice that spontaneously develop tumours in breast tissue. When the tumours had reached a size of 5 mm, they injected a virus that expressed CRABPII and compared the results with mice that received an empty virus vector.

The investigators found that treatment with CRABPII slowed tumour growth in the presence of very low concentrations of RA. 'We noted that the protein has a very significant effect, even if you do not treat the mice with RA at all,' adds Noy. This would imply that the endogenous levels of RA in the body are sufficient to cause a therapeutic effect in the presence of CRABPII.

The results are particularly encouraging because treatment with RA is associated with toxicity at therapeutic doses. However, Noy's strategy comes with its own problems that need to be solved before this can become a therapeutic option in humans. 'Noy used adenoviral vectors to express CRABII in the transgenic mice,' says Altucci. 'This approach has been pursued for some time by pharmaceutical companies for somatic gene therapy but with little success, mainly due to the virus-elicited immune response.' Noy agrees that, 'this is the main problem therapies like this are going to face – how do you introduce a particular gene to a particular tissue? We need somebody to come up with a reliable technology to introduce genes to target tissues.'

## Implications for other diseases

This new strategy might have important applications in other diseases as well. Noy suggests that other lipophilic signaling molecules might act via mechanisms similar to that observed with RA. In fact, she found that fatty-acid-binding proteins (FABPs) enhance the transcriptional activity of PPARs (transcription factors activated by fatty acids) in a similar fashion to CRABPII and RARs [3].

PPARs are important drug targets: PPAR-γ plays an key role in the development of type 2 diabetes, atherosclerosis and certain cancers, whereas PPAR-α is involved in the pathogenesis of hyperlipidemia. However, like retinoids that are used to target RARs to treat cancer, therapies targeting PPARs are associated with toxicity. 'One would wonder if we could just bypass the chemical treatment by introducing the correct lipid-binding protein, which will enhance the transcriptional activity of these endogenous and natural ligands,' conceives Noy. 'You might have the same effect.'

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