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# monitor


## MOLECULES

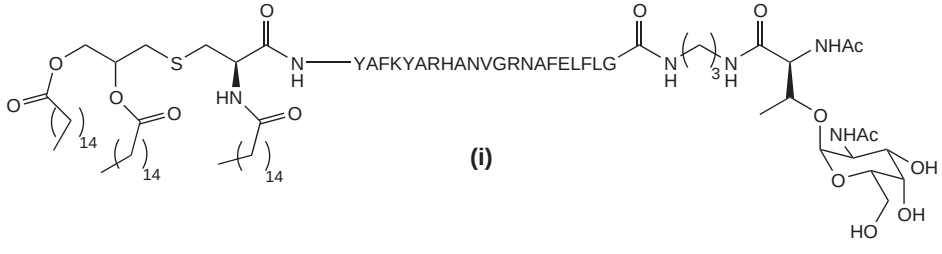
### A synthetic carbohydrate-based anticancer vaccine

The frequent overexpression of oligosaccharides, such as Tn antigens, on the surface of cancer cells promotes metastasis (the process by which tumour cells migrate from their original location), leading to the establishment of secondary (aggressive) tumours at distant sites. The overexpression of tumour-associated oligosaccharides has prompted the development of cancer vaccines, although previous attempts to develop vaccines have been difficult as a result of the limited immunogenicity of saccharides, because they alone cannot activate T helper cells. This activation is required, in conjunction with B cells, for the production of effective antibodies. Alternative strategies are therefore required for the presentation of tumour-associated carbohydrate T epitopes, peptide fragments that can activate T helper cells and lead to more-efficient generation of the IgG class of antibodies.

Buskas and co-workers [1] have reported the development and evaluation of a synthetic anticancer vaccine candidate **(i)** comprising the minimal structural features required for an effective T-cell-dependent immune response. The structural features are:

- tumour-associated Tn antigen, overexpressed on the surface of breast, colon and prostate epithelial tumour cells, but not on normal cells.
- peptide T epitope YAFKYARHANVGRNAFELFL (YAF), to induce a T-cell-dependent immune response resulting in the production of IgG antibodies against the Tn antigen.
- lipopeptide *S*-[*R*-2,3-dipalmitoyloxypropyl]-N-palmitoyl-*R*-cysteine ($Pam_3Cys$), a powerful immunoadjuvant that leads to the production of pro-inflammatory cytokines and chemokines, in turn initiating development and activation of T helper cells; in addition the lipopeptide was expected to facilitate the incorporation of the antigen into liposomes, useful vectors in vaccine design with low intrinsic immunogenicity.

The tricomponent system **(i)** was incorporated into phospholipid-based liposomes and groups of female BALB/c mice were immunized subcutaneously with the freshly prepared liposomes (containing 0.6 μg carbohydrate) at weekly intervals. Mice immunized with the liposome preparation of **(i)** were found to elicit IgM and IgC antibodies against the Tn antigen; the presence of IgG antibodies indicated that the T helper epitope peptide of **(i)** had activated T helper lymphocytes. These proof of principle studies for the use of lipidated glycopeptides as vaccine candidates are a significant advance in the field and further improvements to this tricomponent system are eagerly awaited.




**(i)**

1 Buskas, T. *et al.* (2005) Towards a fully synthetic carbohydrate-based anticancer vaccine: synthesis and immunological evaluation of a lipidated glycopeptide containing the tumor-associated Tn antigen. *Angew. Chem. Int. Ed.* 44, 5985–5988

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### An inhibitor of insulin-like growth factor-1 receptor kinase with in vivo antitumour activity

Intracellular signalling through the insulin-like growth factor-1 receptor (IGF-1R) results in the activation of the Ras–Raf–MEK and the PI3K–Akt pathways, two important and well-studied pathways in tumourigenesis [2]. Epidemiological studies have correlated elevated levels of the IGF-1R ligand (IGF-1) with an increased risk of developing colon, breast, prostate and lung cancer. For these reasons, antagonism of IGF-1R signalling has become a major focus in the search for new antitumour agents in recent years [3]. One important challenge in the development of IGF-1R inhibitors is thought to be achieving selectivity for IGF-1R over the closely related insulin receptor (there is 84% sequence homology in the tyrosine kinase domain).

Encouraged by the emerging target validation data available for IGF-1R, Wittman and co-workers (Bristol-Myers Squibb) [4] have embarked on an IGF-1R antagonist discovery programme. Initial screening led to the identification of benzimidazole **(ii)** as an ATP-competitive inhibitor of IGF-1R ($IC_{50}$ = 3.5 μM).



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