Designing a new generation of anti-hCG vaccines for cancer therapy

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Introduction: The hCG hormone is normally only present in readily detectable amounts in the circulation during pregnancy. However, a number of different types of cancer are reported to aberrantly express hCGβ. Thus, hCG-based vaccines have application for the treatment of a variety of cancers as well as providing a novel method of family planning. The vaccines which are currently available may benefit from enhancing their immunogenicity. Furthermore, whilst not a feature of the vaccine which utilizes only the C-terminal peptide of hCGβ, some other hCG-based vaccines contain cross-reactive β-chain epitopes that provoke potentially harmful antibodies due to reactivity with LH. We have therefore sought to develop novel hCG-based vaccines with enhanced characteristics.

Methodology: PCR-based mutagenesis was used to introduce one or more amino acid replacements in the sequence of hCGβ. The selected substitutions were chosen based upon the sequence of the CG β-chain in other species, and of the β-chain sequence in human LH, FSH and TSH. The main aim of this strategy was to conserve the folding of the molecule by selecting amino acids that were present in other β-chains, whilst at the same time attempting to remove amino acids contributing to CG/LH cross-reactive epitopes. Mutated sequences were cloned into a baculovirus expression vector and then expressed in Sf9 insect cells. The vaccine candidate molecules were subsequently affinity purified from the culture supernatants.

Results and Discussion: A large number of mutants have been generated and analyzed for their antigenicity. One mutant (hCGβR68E), in which the arginine at position 68 has been replaced with a glutamic acid, has substantially lost cross-reactivity with LH. This molecule has been subjected to extensive immunogenic analysis in mice and rabbits, using protein immunization via both injection and mucosal routes, and DNA immunization. When combined with an appropriate carrier and adjuvant it is able to generate an antibody response which is focused onto hCG-unique epitopes, including a much more potent response against the CTP than that obtained with the wild-type hCGβ-chain.

Conclusions: We have generated a novel molecule, hCGβR68E, which provokes an hCGβ-specific antibody response with characteristics that may be highly advantageous for application in both family planning and tumor immunotherapy.