Fuad Fares, Adv Genet Eng 2013, 2:3
http://dx.doi.org/10.4172/2169-0111.S1.004

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Genetic Engineering & Genetically Modified Organisms
August 12-13, 2013 DoubleTree by Hilton, Raleigh, NC, USA

Developing long acting analogs of glycoprotein hormones using site-directed mutagenesis, gene fusion and gene transfer

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Glycoprotein hormones are used clinically in the treatment of many diseases. One major issue regarding the clinical use of many peptides is their short half-life due to the rapid clearance from the circulation. The major strategies for overcoming this problem by pharmaceutical companies are based on chemical techniques. To overcome this problem, we used genetic engineering techniques that have been found successful for designing long acting hormones. By using overlapping PCR techniques, we succeeded to add the signal sequence of O-linked oligosaccharides to the coding sequence of the hormones. The cassette gene that has been used contains the sequence of the carboxyl-terminal peptide (CTP) of human chorionic gonadotropin β (hCGβ) subunit. The CTP contains 28 amino acids with four O-linked oligosaccharide recognition sites. It was postulated that the O-linked oligosaccharides add flexibility, hydrophilicity and stability to the protein. On the other hand it was suggested that the four O-linked oligosaccharides play an important role in preventing plasma clearance and thus increasing the half-life of the protein in circulation. Using this strategy we succeeded to ligate the CTP to the coding sequence of follitropin (FSH), thyrotropin (TSH), erythropoietin (EPO) growth hormone (GH) and thus to increase the longevity and bioactivity of these proteins in-vivo. Interestingly, the new analog of FSH was found not immunogenic in humans and it is already passed successfully clinical trials phase III. Moreover, FSH long acting was approved by the European Commission (EC) for treatment of fertility. In addition, our results indicated that long acting GH is not toxic in monkeys and the results from clinical trials phases I and II seem to be promising. Designing long acting peptides will diminish the cost of these drugs and perhaps reduce the number of injections in the clinical protocols.

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