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

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Abstract

One major issue regarding the clinical use of many peptides is their short half-life due to the rapid clearance from the circulation. To overcome this problem, we used overlapping PCR technique to add the signal sequence of *O*-linked oligosaccharides to the coding sequence of glycoprotein hormones. The used cassette gene 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.

Biography

Prof. Fares has completed his Ph.D at the age of 30 years from the Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel, and postdoctoral studies from Washington University, School of Medicine, Saint Louis, MO, USA. He is the director of The Department of Molecular Genetics, Carmel Medical Center, and associated professor at the Department of Human Biology, Faculty of Natural Sciences, University of Haifa. He has published more than 80 papers in reputed journals and the founder of PROLOR Biotech Company.