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Biography

Fuad Fares has completed his MSc and DSc studies at the Faculty of Medicine, Technion-Israel Institute of Technology, and postdoctoral studies at the Department of Molecular Biology and Pharmacology, School of Medicine, Washington University, St. Louis Missouri. He developed the Department of Molecular Genetics at Carmel Medical Center and lead this department last 20 years. He is Associate Professor at the Department of Human Biology, University of Haifa and head the Laboratory of Molecular Genetics. He has published more than 90 manuscripts in reputed journals and served as a Member of the Israel Council for Higher Education last 15 years. He is the founder of PROLOR Biotech company for designing long acting recombinant proteins and CanCurX for identification of natural products for treatment of cancer.

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NOVEL STRATEGY FOR DESIGNING LONG-ACTING RECOMBINANT PROTEINS FOR CLINICAL USE

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 succeeded to ligate 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 (hCG) subunit. The CTP contains 28 amino acids with four O-linked oligosaccharide recognition sites. It was postulated that 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 analogs of FSH and GH were found not immunogenic in human and it is already passed successfully clinical trials phase III and phase II respectively. Moreover, FSH long acting (ELONVA) was approved by the European Commission (EC) for treatment of fertility since 2010. In addition, our results indicated that long acting GH is not toxic in monkeys and the results from clinical trials phase I and phase 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. On the other hand, we found that deletion of N-linked oligosaccharides from hTSH subunits resulted in significant decreased in the bioactivity. Moreover, deglycosylated variants of TSH compete with normal hTSH and human thyroid stimulating immunoglobulin (hTSI) in a dose dependent manner. Thus, this variant, behaves as potential antagonist, who may offer a novel therapeutic strategy in the treatment of Grave's disease, the most common form of hyperthyroidism. In conclusion, it was found that addition of O-linked oligosaccharides or deletion of N-linked oligosaccharides could be interesting strategy for designing new analogs of glycoprotein hormones.



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