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Growth hormone administration patterns differently regulate epidermal growth factor signaling

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Growth hormone (GH) is a pituitary hormone that stimulates longitudinal bone growth and induces diverse effects on cell growth, differentiation, and metabolism of proteins, lipids and carbohydrates (Herrington & Carter-Su 2001). The use of growth hormone in the endocrine practice and for the treatment of various clinical conditions is expanding. The first use of human GH (hGH) was replacement therapy in children with GH deficiency (GHD). However, further indications have been gradually approved or proposed since the development of recombinant human GH (rhGH). Current protocols for growth hormone treatment imply its subcutaneous or intramuscular injection once daily or three times a week. Main disadvantages of these administration protocols rely on the short plasma half life of the hormone and on its renal toxicity. Moreover, injection results in poor patient compliance, high dose, non-specific toxicity and increased cost. Thus, development of sustained-release rhGH formulations could improve patient quality of life and decrease secondary effects. To date, a once-weekly sustained release GH preparation has shown to be effective for the treatment of several clinical conditions and sustained delivery systems that last longer are being investigated. However, GH shows differential effects depending on its plasma concentration pattern in many species including mice, rats and humans. Therefore, the efficacy and toxicity of pharmaceutical systems that allow prolonged release of the hormone, which would produce near continuous GH circulating levels, should be assessed and compared with the effects of the treatments that involve intermittent injections and mimic a pulsatile concentration pattern. A relevant side effect associated with chronic use of GH and its overexpression is the increased risk of malignancies. Previous studies suggested that plasma growth hormone patterns regulate epidermal growth factor receptor (EGFR) expression in rodent liver. The

EGFR, also known as ErbB-1, is a plasma membrane glycoprotein which belongs to the ErbB family of receptor tyrosine kinases (RTKs) (Burgess 2008). Upon ligand binding, ErbB proteins homo- or heterodimerize with other members of the ErbB family to activate downstream signaling pathways that regulate proliferation, growth, and differentiation (Riese & Stern 1998). Aberrant expression of the EGFR and/or hyperactivation of this receptor have been associated with pathogenesis and progression of different types of cancers.

Therefore, considering the growing interest in developing sustained delivery systems for GH administration, the potential oncogenic properties of this hormone and its likely dimorphic regulation of a receptor widely involved in cancer, the EGFR, the aim of this presentation was to analyze the effects of different GH administration protocols on EGFR expression, signaling and induction of mitogenic mediators in the liver of normal mice.

Current growth hormone (GH) administration protocols require frequent subcutaneous injections, resulting in suboptimal compliance. Therefore, there is interest in developing delivery systems for sustained release of the hormone. However, GH has different actions depending on its continuous or pulsatile plasma concentration pattern. GH levels and circulating concentration patterns would be involved in the regulation of epidermal growth factor receptor (EGFR) expression in liver. Aberrant expression of this receptor and/or its hyperactivation has been associated with pathogenesis of different carcinoma types. Considering that one of the adverse effects associated with GH overexpression and chronic use of GH is the increased incidence of malignancies, the aim of this study was to analyze the effects of GH plasma concentration patterns on EGFR expression and signaling in mice liver. For this purpose, GH was administered by subcutaneous daily injections to produce an intermittent GH plasma pattern or by osmotic pumps to provoke a continuous concentration pattern. Results showed that intermittent injections of GH induced an up-regulation of liver EGFR content, augmented the response to EGF and the induction of proteins involved in cell proliferation promotion in female mice. On the contrary, continuous GH delivery had the opposite effects in male mice: EGFR liver content diminished as well as the

response to exogenous stimulation of EGFR signaling and induction of early genes. Results suggest that sustained delivery systems that allow continuous GH plasma patterns would be beneficial in terms of treatment safety referred to its actions over EGFR signaling and its promitogenic activity.