SOM230: A new therapeutic modality for Cushing’s disease

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The somatostatin (SRIF, somatotropin release inhibiting factor) field has been a success story in terms of medicinal chemistry and drug discovery offering a variety of therapeutic opportunities, e.g. acromegaly, gastrointestinal neuroendocrine tumors, whole body imaging and radiotherapy. Indeed, a rational medicinal chemistry approach capitalising on structure activity relationships led to the discovery of SOM230, a stable cyclohexapeptide somatostatin mimic which exhibits unique binding to human SRIF receptors (sst1-5). This approach involved transposing functional groups, in the form of unnatural amino acids, from SRIF-14 into the stable, reduced size cyclohexapeptide template. Further, the hydroxyproline urethane extension of SOM230 has been functionalized with the chelators DTPA and DOTA, which is a necessary prerequisite for the possible development of ligands which could be used for whole body imaging. Uniquely, SOM230 exhibits binding with a 30 to 40 times higher affinity than Sandostatin® to the sst1 and sst5 receptors and exhibits higher efficacy in preclinical models in lowering Growth Hormone, Insulin-Like Growth Factor-1, ACTH and corticosterone than Sandostatin®. Recently, phase III clinical studies have established the therapeutic potential of SOM230 / Pasireotide (Signifor®), as the first pituitary directed medical therapy for Cushing’s disease\(^1\) leading to registration of SOM230 by both EMEA and FDA in 2012.