The dopastatin BIM-23A760 distinctly influences key functional endpoints in different types of pituitary adenomas and normal pituitaries: role of somatostatin and dopamine receptor profile

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Justo P. Castaño[1]*, Alejandro Ibáñez-Costa[1], Laura Mª López-Sánchez[1,2], Manuel D. Gahete[1], Esther Rivero-Cortés[1], Mª Carmen Vázquez-Borrego[1], Mª Ángeles Gálvez[3], Andrés de la Riva[4], Eva Venegas-Moreno[5], Luis Jiménez-Reina[6], Alberto Moreno-Carazo[7], Francisco J. Tinahones[8], Silvia Maraver-Selfa[8], Miguel A. Japón[9], Juan A. García-Arnés[10], Alfonso Soto-Moreno[5], Susan M. Webb[11], Rhonda D. Kineman[12], Michael D. Culler[13], Raúl M. Luque[1]*.

[1]Department of Cell Biology, Physiology and Immunology, University of Cordoba (UCO), Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofia (HURS); CIBER Fisiopatología de la Obesidad y Nutrición; and Campus de Excelencia Internacional Agroalimentario (ceiA3); Córdoba, Spain; [2]Research Unit, UCO/IMIBIC/HURS, Córdoba Spain; [3]Service of Endocrinology and Nutrition, HURS/IMIBIC, Córdoba, Spain; [4]Service of Neurosurgery, HURS, Córdoba, Spain; [5]Metabolism and Nutrition Unit, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, Sevilla, Spain; [6]Department of Morphological Sciences, UCO, Córdoba, Spain; [7]Endocrinology and Nutrition Unit, Complejo Hospitalario de Jaén, Jaén, Spain; [8]Service of Endocrinology and Nutrition, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain; [9]Department of Pathology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [10]Department of Endocrinology and Nutrition, Carlos Haya Hospital, Málaga, Spain; [11]Department of Endocrinology, Hospital Sant Pau, Centre for Biomedical Research on Rare Diseases (Centro de Investigación Biomédica en Red de Enfermedades Raras Unit 747) Autonomous University of Barcelona; Barcelona Spain; [12]Department of Medicine, University of Illinois at Chicago, Jesse Brown Veterans Affairs Medical Center, Research and Development Division, Chicago, Illinois, USA;[13]IPSEN Bioscience, Cambridge, MA, USA.. **These authors codirected this study*

IMIBIC MAIMONIDES BIOMEDICAL RESEARCH INSTITUTE OF CORDOBA

UNIVERSIDAD DE CÓRDOBA · Servicio Andaluz de Salud CONSEJERÍA DE SALUD · Hospital Universitario Reina Sofía

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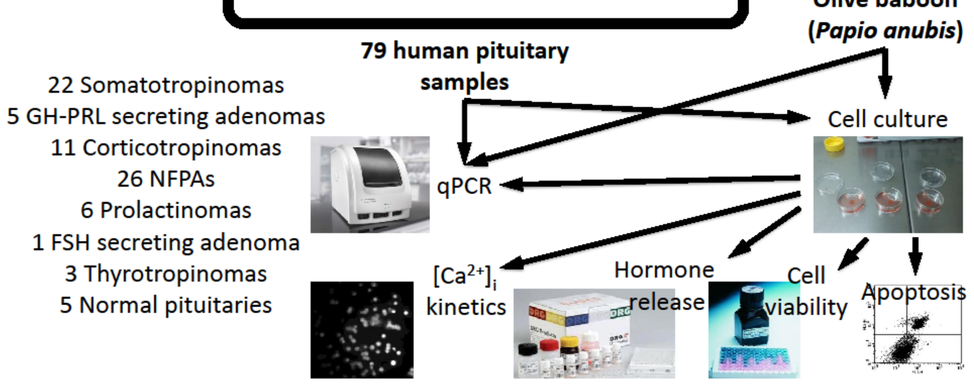
Introduction

Chimeric somatostatin (SST)/dopamine (DA) compounds, termed dopastatins, such as **BIM-23A760**, an agonist of somatostatin (sst2, sst5) and dopamine (D_2) receptors, are emerging as promising novel alternatives for the treatment of **pituitary adenomas**. However, their exact actions and precise mechanisms on the different types of pituitary tumors are still to be fully understood.

Thus, the **aim of this study** was to analyze a set of key **functional parameters** (signaling pathways, hormone expression and secretion, cell viability and apoptosis), **in response to BIM-23A760** in a series of 74 human pituitary adenomas, 5 normal and 3 olive baboon pituitary samples (as a relevant non-human primate model).

Materials & Methods



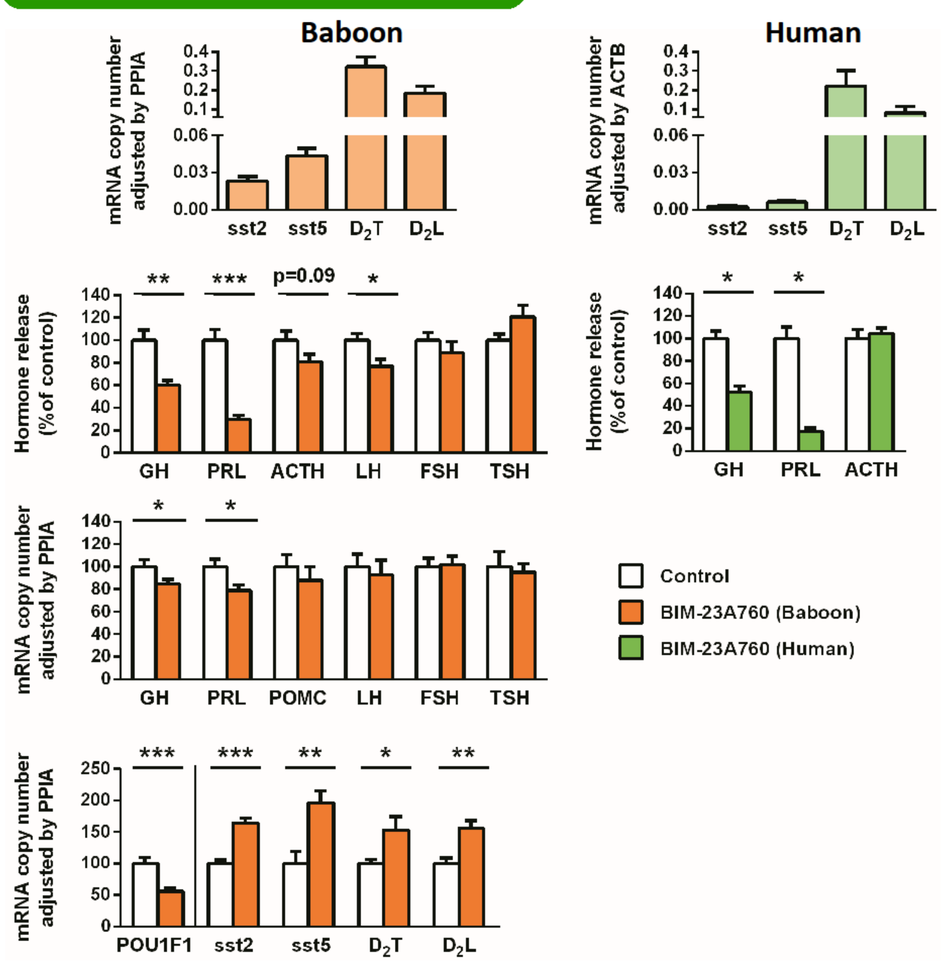
Normal pituitary

We found that **sst5, sst2 and D_2** were **highly expressed** in both **baboon** and **human pituitaries**, and their expression was virtually identical in both species.

D_2T> D_2L>sst5>sst2.

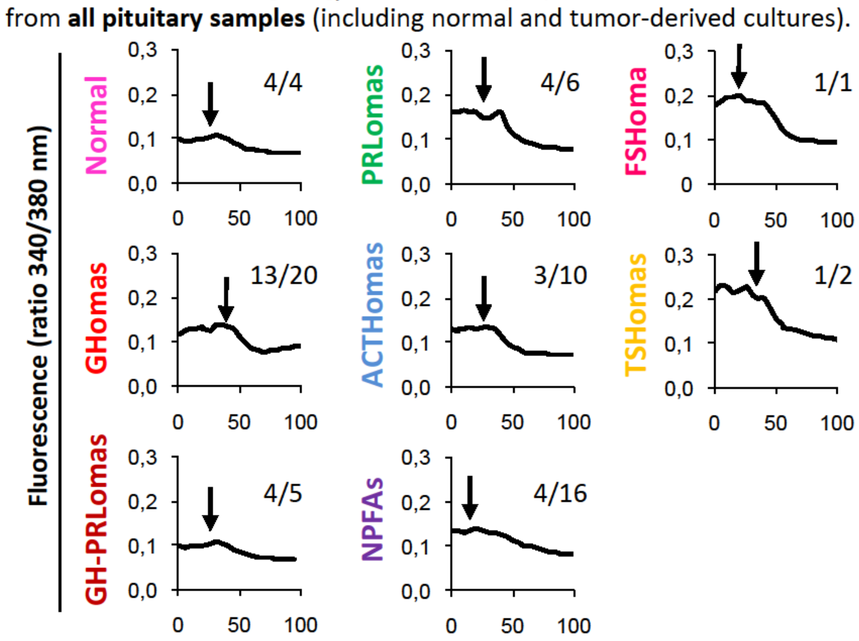
We observed a decrease of **GH** and **PRL release** in response to BIM-23A760 in human and baboon normal pituitary primary cultures, as well as a significant **decrease** in **LH** and a slight **inhibition** in **ACTH release** in the case of baboon pituitary cell cultures.

Additionally, in primate primary cultures, we observed a **decrease** in **GH** and **PRL** at **mRNA** levels, which was supported by a significant **repression** of **POU1F1**; but interestingly, we also observed an **up-regulation** of **sst2**, **sst5**, **D_2T** and **D_2L** expression.

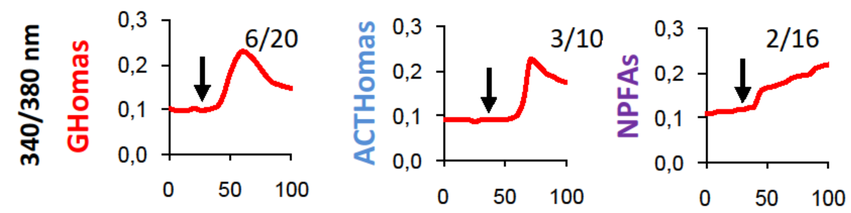


Ca^{2+} signaling

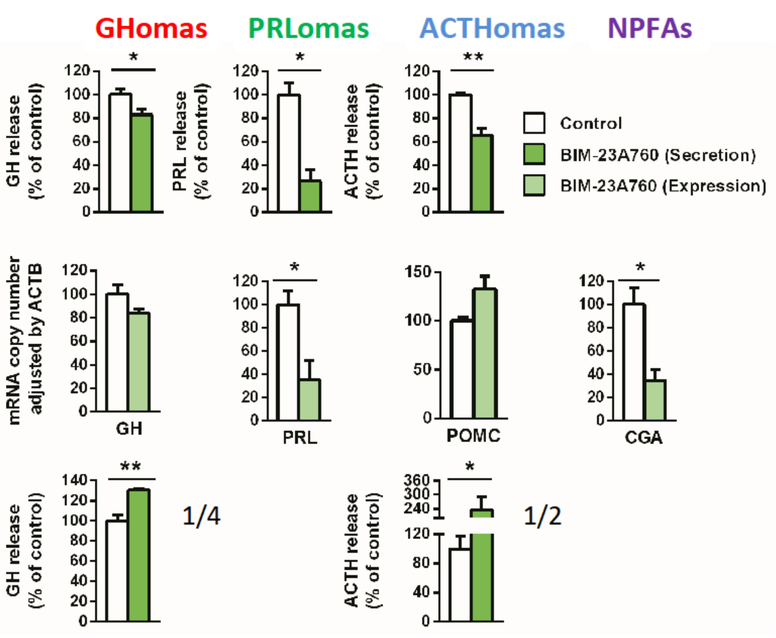
BIM-23A760 **inhibited $[Ca^{2+}]_i$** in a different proportion of the cell cultures tested from **all pituitary samples** (including normal and tumor-derived cultures).



Interestingly, we also found that BIM-23A760 **increased $[Ca^{2+}]_i$** in 30% of **GHomas** and **ACTHomas**, and in 13% of the **NFPAs** analyzed



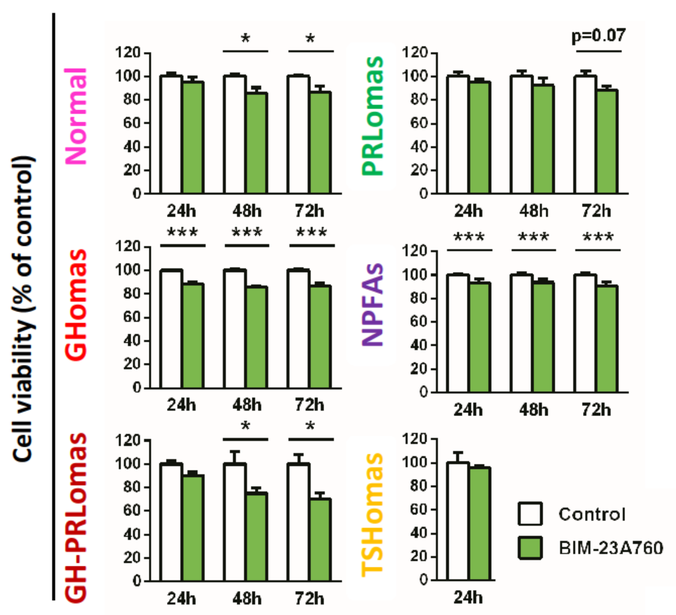
Hormone release/expression



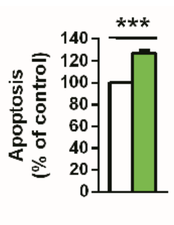
BIM-23A760 **inhibited** GH release in the majority of **GHomas**, PRL expression/release in all **PRLomas,** ACTH release in **ACTHomas**, and CGA expression in **NFPAs.**

However, BIM-23A760 **increased hormone release** in certain proportion of **GHomas** and **ACTHomas**

Cell viability



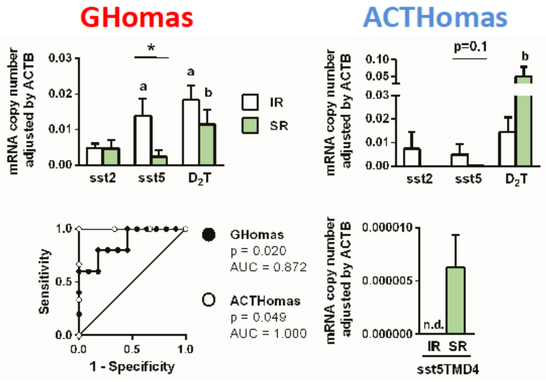
GHomas



BIM-23A760 **inhibited cell viability** in **normal pituitary,** and **in** most of **pituitary adenoma** subtypes.

Additionally, BIM-23A760 also **increased apoptotic rate** in **somatotropinomas**

Molecular profile



We observed a markedly **lower expression of sst5** in *stimulatory responders* compared with *inhibitory responders,* in both **GH-** and **ACTH-omas**, which might serve as a predictor of such response, as indicated by ROC analyses.

In addition, in **ACTHomas**, *stimulatory responders* expressed **sst5TMD4**, while no expression was detectable in *inhibitory responders*.

Conclusion

Altogether, our results reinforce the notion that chimeric dopastatins (e.g. BIM-23A760) can affect multiple, clinically relevant parameters on most types of pituitary adenomas and may represent new therapeutic tools to treat pituitary tumors, wherein the relative SST/DA receptor expression profile might provide useful molecular markers to predict the ultimate response of these tumors to BIM-23A760.

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