

Conferencia:
**PDE10A Inhibitors as Potential
Treatments for Schizophrenia**

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Toledo - España

16/07/15

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XUNTA DE GALICIA

CONSELLERÍA DE CULTURA, EDUCACIÓN
E ORDENACIÓN UNIVERSITARIA



PDE10A INHIBITORS AS POTENTIAL TREATMENTS FOR SCHIZOPHRENIA

Schizophrenia is a severe mental disorder characterized by a combination of positive (e.g., hallucinations and delusions), negative (e.g., anhedonia and poverty of speech) and cognitive symptoms.¹ All currently available antipsychotic therapies rely on dopamine D2 receptor antagonism to exert their action and are highly efficacious addressing positive symptoms but ineffective for the other core symptoms of the disease. Furthermore, they are associated with severe side-effects (e.g., Parkinson-like extrapyramidal (EPS) symptoms, prolactin release, weight gain or cardiac risk) which limit patient compliance.² As a result, during the past 10-15 years, several alternative mechanisms of action have been investigated³ aiming for improved antipsychotic medications.

Among these different approaches, inhibition of phosphodiesterase 10A (PDE10A) has been proposed as a potential new avenue for the treatment of schizophrenia supported by the activity of PDE10A inhibitors in preclinical models of positive, cognitive and negative symptoms.

Starting from a HTS campaign, a focused medicinal chemistry optimization has led us to the identification of a series of imidazopyrazine derivatives as a novel class of PDE10A inhibitors. These compounds inhibit PDE10A mediated c-AMP inhibition in vitro and have also proven to be efficacious in preclinical models of schizophrenia. Evolution of our medicinal chemistry program, SAR and SPR analysis as well as a detailed profile for optimized PDE10A inhibitors will be described.

¹ Tandon, R.; Nasrallah, H.A.; Keshavan, M.S. *Schizophr. Res.* 2009, 110, 1–23.

² Conn, J. P.; Lindsley, C. W.; Jones, C. K. *Trends Pharmacol Sci.* 2009, 30, 148-155.

³ Macdonald, G.J.; Bartolome J.M. *Progress in Medicinal Chemistry* 2010, 49, 37-80.

CURRICULUM VITAE

EMPLOYEE NAME: **CARLOS M MARTÍNEZ**

DATE: **27th MAY 2015**

SITE: Toledo (Spain)
DIVISION: Janssen Research and Development
DEPARTMENT: Neuroscience Discovery

EDUCATION:

10/2002-12/2006	PhD in Organic Chemistry with highest honours (Cum Laude) at Universidad de Santiago de Compostela (Spain) under the supervision of Professor Domingo Domínguez. Dissertation (25/01/2008) entitled: "Total synthesis of new quinazolines and quinolines".
10/1997-07/2002	MSc and BSc in Organic Chemistry at Universidad de Santiago de Compostela (Spain)

EMPLOYMENT

10/2008-to date	Scientist, Permanent position, Medicinal Chemistry, Johnson & Johnson PRD-Toledo
05/2007-09/2008	Senior Associated Scientist, Permanent position, Medicinal Chemistry, Johnson & Johnson PRD-Toledo
01/2007-04/2007	Senior Associated Scientist, Temporary position, Medicinal Chemistry, Johnson & Johnson PRD-Toledo

KEY CURRENT JOB RESPONSIBILITIES

Responsible for conducting research directed to the discovery and/or development of therapeutic agents including but not limited to: originating scientific experiments; developing new methodology; maintaining a state-of-the art scientific knowledge; and originating and defending ideas in on-going projects and for new projects.

CURRICULUM VITAE

EMPLOYEE NAME: **CARLOS M MARTÍNEZ**

DATE: **27th MAY 2015**

PUBLICATIONS

Manuscripts

Conde Ceide, Susana; Martinez-Vituro, Carlos M.; Alcazar, Jesus; Garcia-Barrantes, Pedro M.; Lavreysen, Hilde; Mackie, Claire; Vinson, Paige N.; Rook, Jerri M.; Bridges, Thomas M.; Daniels, J. Scott; Menges, Anton; Langois, Xavier; Drinkenburg, Wilhelmus H.; Ahnaou, Abdellah; Niswender, Colleen M.; Jones, Carrie K.; MacDonald, Gregor J.; Steckler, Thomas; Conn, P. Jeffrey; Stauffer, Shaun R.; Bartolome-Nebreda, Jose Manuel; Lindsley, Craig W., "Discovery of VU0409551/JNJ-46778212: An mGlu5 Positive Allosteric Modulator Clinical Candidate Targeting Schizophrenia", *ACS Med. Chem. Lett.*, **2015**, DOI: 10.1021/acsmedchemlett.5b00181

Martin-Martin, Maria Luz; Bartolome-Nebreda, Jose Manuel; Conde-Ceide, Susana; Alonso de Diego, Sergio A.; Lopez, Silvia; Martinez-Vituro, Carlos M.; Tong, Han Min; Lavreysen, Hilde; MacDonald, Gregor J.; Steckler, Thomas; Mackie, Claire; Bridges, Thomas M.; Daniels, J. Scott; Niswender, Colleen M.; Noetzel, Meredith J.; Jones, Carrie K.; Conn, P. Jeffrey; Lindsley, Craig W.; Stauffer, Shaun R., "Discovery and SAR of novel series of imidazopyrimidinones and dihydroimidazopyrimidinones as positive allosteric modulators of the metabotropic glutamate receptor 5 (mGlu5)", *Bioorg. & Med. Chem. Lett.*, **2015**, 25 (6), 1310-1317

Bartolome-Nebreda, Jose Manuel; Alonso de Diego, Sergio A.; Artola, Marta; Delgado, Francisca; Delgado, Oscar; Martin-Martin, Maria Luz; Martinez-Vituro, Carlos M.; Pena, Miguel Angel; Tong, Han Min; Van Gool, Michiel; Alonso, Jose Manuel; Fontana, Alberto; Macdonald, Gregor J.; Megens, Anton; Langlois, Xavier; Somers, Marijke; Vanhoof, Greet; Conde-Ceide, Susana, "Identification of a Novel Orally Bioavailable Phosphodiesterase 10A (PDE10A) Inhibitor with Efficacy in Animal Models of Schizophrenia", *J. Med. Chem.*, **2015**, 58 (2), 978–993

José Manuel Bartolomé-Nebreda, Francisca Delgado, María Luz Martín-Martín, Carlos M. Martínez-Vituro, Joaquín Pastor, Han Min Tong, Laura Iturrino, Gregor J. Macdonald, Wendy Sanderson, Anton Megens, Xavier Langlois, Marijke Somers, Greet Vanhoof, and Susana Conde-Ceide, "Discovery of a Potent, Selective, and Orally Active Phosphodiesterase 10A

CURRICULUM VITAE

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Inhibitor for the Potential Treatment of Schizophrenia", *J. Med. Chem.*, **2014**, 57 (10), 4196–4212

C. M. Martínez-Vituro, D. Domínguez, "Synthesis of new chromeno[4,3,2-*d,e*]quinazolin-2-ones, -quinazolines and -pyrrolo[2,1-*b*]quinazolines", *J. Heterocyclic Chem.* **2007**, 44, 1035.

C. M. Martínez-Vituro, D. Domínguez, "Synthesis of aza analogues of the anticancer agent batracylin", *Tetrahedron Lett.* **2007**, 48, 4707.

C. M. Martínez-Vituro, D. Domínguez, "Synthesis of the antitumoural agent batracylin and related isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones.", *Tetrahedron Lett.* **2007**, 48, 1023.

PROFESSIONAL PRESENTATIONS

Lecture at: **Workshop on Drug Discovery, Clinical Trials and Human Applications**, June 28-29, 2011, Toledo, Spain

Oral communication at: **XXI Reunión Bienal de Química Orgánica**, September 18-20, **2006**, Valladolid, Spain.

Poster presentation at: **XXX Reunión Bienal de la RSEQ**, September 19-23, **2005**, Lugo, Spain.

Poster presentation at: **5th Spanish Italian Symposium on Organic Chemistry**, September 10-13, **2004**, Santiago de Compostela, Spain

