PONTIFICIA ACADEMIA SCIENTIARVM

THE AWARD

OF THE

PIUS XI GOLD MEDAL

2008

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The aim of the Pontifical Academy of Sciences, which was founded on 28 October 1936 by the Holy Father Pius XI, is to honour pure science, wherever this may be found, to ensure its freedom, and to support the research essential for the progress of applied science.

On 28 October 1961, on the occasion of the XXVth anniversary of the foundation of the Pontifical Academy of Sciences, the Holy Father John XXIII established the Pius XI Gold Medal in honour of the founder of the Academy. The medal should be awarded to a young scientist who has already gained an international reputation.

The Council of the Academy unanimously decided to award the "Pius XI Gold Medal" for the year 2008 to

Prof. JUAN A. LARRAÍN

in recognition of his great merits as a scholar and the important contribution of his research to scientific progress.


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JUAN A. LARRAÍN
A.D.
MMVIII

JUAN A. LARRAÍN

BIOGRAPHICAL DATA

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Designation: Professor

Professional Address:
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Santiago, Chile

Date of Birth: 15 January 1970

Place of Birth: Santiago, Chile

Wife and Children: Married to Marcela; Marcela, Jacinta, Trinidad and Elisa

Academic Qualifications:
B.Sc. (Biochemistry)
P. Universidad Católica de Chile (1993)

Ph.D. (Cell and Molecular Biology)
P. Universidad Católica de Chile (1998)

Pew Latin American Postdoctoral Fellowship (1998-2000)
Howard Hughes Medical Institute
University of California, Los Angeles, USA

Previous Positions:
Research Associate (2000-2002)
Howard Hughes Medical Institute
University of California, Los Angeles, U.S.A.

Assistant Professor (2002-2006)
Center for Cell Regulation and Pathology
Faculty of Biological Sciences
P. Universidad Católica de Chile

Current Professional Activity:

Associate Professor (2006–)
Center for Cell Regulation and Pathology
Faculty of Biological Sciences
P. Universidad Católica de Chile

Chair (2005–)
PhD Program in Cell & Molecular Biology
Faculty of Biological Sciences
P. Universidad Católica de Chile

Membership of Professional Societies:

Latin-American Society for Developmental Biology (Treasurer)

Young Affiliated Member, Third World Academy of Science (TWAS)

Sociedad Chilena de Biología Celular

Society for Developmental Biology

Awards (National):

(1993) Best graduate student of the 1988 Class in Biochemistry, P. Universidad Católica de Chile

(1994-1998) "Fundación Andes" Ph.D. Fellowship

(1999) Ph.D. Thesis Award, Chilean Academy of Science

(1999) PhD Thesis Award, Chilean Society for Cell Biology

(2004-2006) Member of the Program: "Frontiers of Science", Chilean Academy of Science

(2006) Young Scientist Prize from Bios-Chile and "Sociedad Chilena de Biología"

Awards (International):

(1998-2000) Pew Latin American Postdoctoral Fellow

(2007) TWAS ROLAC Young Scientist Award in Biological Sciences

Speaker at International Conferences:

1st International Meeting, Latin American Society of Developmental Biology. January 13-18, 2003. Valle Nevado, Chile.

10th International Xenopus Meeting. September 14-18, 2004. Woods Hole, Massachusetts, USA

2nd International Meeting, Latin American Society of Developmental Biology. May 4-7, 2005. Guarujá, Brazil.

12th Congress of the International Association of Catholic Medical Schools. May 11-13, 2005. Seoul, South Korea.

Gordon Conference in Developmental Biology, June 19-24, 2005. New Hamphshire, USA

BSDB Fall Meeting "Wnt signaling in Development, Disease and Cell Biology". September 14-16, 2005. Aberdeen, Scotland.

International Workshop "Latest Concepts in Developmental Biology". April 20-23, 2006. Córdoba, Argentina.

Gordon Conference in Proteoglycans. July 9-14, 2006. New Hampshire, USA

TWAS-ROLAC First Regional Conference of Young Scientists (RCYS): Promoting Life Sciences for Sustainable Development. September 1-6, 2006. Rio de Janeiro, Brazil.

11th International Xenopus Conference. September 12-16, 2006. Tokyo, Japan.

Simposio da America Latina e Caribe para Jovens Cientistas TWAS-ROLAC. Reuniao Magna da Academia Brasileira de Ciencias. May 29-31, 2007. Rio de Janeiro, Brazil.

Society for Developmental Biology, 66th Annual Meeting. Latin American Society for Developmental Biology, 3rd Annual Meeting. June 16-20, 2007. Cancún, México.

TWAS 18th General Meeting. November 13-14, 2007. Trieste, Italy.

Santa Cruz Developmental Biology. June 26-29, 2008. Santa Cruz, USA.

12th International Xenopus Conference. September 8-12, 2008. Germany.

2nd EMBO Conference Series. Molecular and cellular basis of regeneration and tissue repair. October 5-9, 2008. Palma de Mallorca, Spain.

BRIEF ACCOUNT OF SCIENTIFIC ACTIVITY

From the beginning of my scientific career I was attracted by Developmental Biology, an area dedicated to understanding how an animal is constructed from a simple egg. After finishing my PhD and during the last ten years I have been working on this field, first as a postdoctoral fellow in Dr. Edward De Robertis' laboratory (Howard Hughes Medical Institute, UCLA, Los Angeles, USA) and, since September 2002, as an independent researcher at the P. Universidad Católica de Chile. Here I will briefly summarize my scientific activities and contributions during this period of time.

One of the key questions in developmental biology is to understand in molecular and cellular terms how an apparently homogeneous cellular territory can acquire specific patterning during the early steps of embryonic development. In 1924 Spemann and Mangold performed transplantation experiments in salamander embryos and found that a small group of cells found in the gastrula stage embryo, later named Spemann's organizer, contain all the information necessary to organize and pattern the surrounding cells into a completely normal embryo. Many of the genes responsible of Spemann's organizer activity have been identified (11).

Chordin, one of Spemann's organizer genes, was isolated in the De Robertis laboratory. Chordin is a secreted protein that binds the morphogen BMP4 in the extracellular space and regulates dorsoventral patterning during early embryonic development. During my postdoctoral fellowship I focused on understanding the biochemical properties of chordin and how it regulates BMP signaling together with other extracellular components. We identified chordin domains as new protein modules that bind and regulate BMP4 signaling. We found that these protein modules are present in other proteins and define a new model for extracellular regulation of growth factor signaling (9, 12). In addition, together with other colleagues, we studied the role of twisted gastrulation (tsg), a gene first identified in *Drosophila* because of its role in dorso-ventral patterning. I demonstrated biochemically that tsg binds BMP and chordin forming ternary complexes. These results led us to propo-

se that tsg modulates Chordin activity and is a key player in establishing a BMP signaling gradient in dorso-ventral patterning (10, 15, 18). In short, during my postdoctoral fellowship I contributed to understanding the biochemical mechanism involved in extracellular regulation of morphogen gradients.

In September 2002 I started my own independent laboratory. During these years as an independent investigator we have focused on understanding the role of Proteoglycans in the early development of the vertebrate embryo. First we identified biglycan as a novel player in dorso-ventral patterning. Biochemical experiments showed that biglycan regulates BMP signalling in the extracellular space though a Chordin-dependent mechanism (19). The importance of this finding is two fold. On the one hand we demonstrated for the first time that biglican, a component of bone extracellular matrix, can regulate BMP activity. In addition, we introduced biglican as a further step in the fine tuning of chordin activity.

We have also studied syndecan4, a cell-surface heparan sulphate proteoglycan. We have demonstrated through *gain* and *loss of function* experiments that syndecan-4 regulates gastrulation and neural tube closure in *Xenopus* embryos. In addition, biochemical experiments showed that syndecan4 binds dishevelled and regulate non-canonical Wnt signalling. These findings are conceptually important because syndecan4 is a component of focal adhesion sites and links Wnt signalling with cell adhesion, an area that has not been completely explored. We have proposed a novel mechanism whereby the presence of syndecan4 and its ability to bring information from the extracellular matrix (fibronectin) could be instrumental for specific activation of the non-canonical Wnt branch (21). The discovery that syndecan4 regulates neural tube closure also has some biomedical implications. Neural tube closure defects are one of the most common malformations in newborns, particularly spina bifida. Understanding how the neural tube closes at the cellular and molecular levels could provide important information in order to approach this medical problem. For those reasons we are currently starting to study the role of syndecan4 in neural tube closure in mouse embryos.

Most of the genes involved in the establishment and function of the Spemann Organizer were identified using pre-genomic era approaches. In the post-genomic era, global analyses of the trans-

ciptome using high-throughput techniques have arrived at the unexpected conclusion that almost 70% of the transcriptome is active in transcription. To have a more comprehensive knowledge of the transcripts involved in Spemann's organizer function we performed a global analysis of the *Xenopus* transcriptome. For this we took advantage of the availability of the *Xenopus* tropicalis genomic sequence and carried out a high-throughput analysis using the technique denominated Serial Analysis of Gene Expression (SAGE). Through this approach we have identified completely novel transcripts expressed differentially at the gastrula stage (26). We are currently studying the function of these transcripts in the early development of the vertebrate embryo.

More recently we started research on Regenerative Biology, a field dedicated to understanding the molecular and cellular mechanisms of regeneration in model organisms. Particularly we are working on understanding the molecular and cellular mechanism of spinal cord regeneration in *Xenopus* tadpoles. Damage to the central nervous system (CNS) in mammals is devastating because of the poor capacity of central neurons to regenerate. In contrast amphibians, including *Xenopus* tadpoles, have a great ability to regenerate parts of their CNS such as the spinal cord. Understanding how spinal cord regeneration takes place in amphibians could provide new pathways to stimulate endogenous regeneration in mammalian CNS. We have found that hyaluronic acid, an extracellular matrix component, is required for proper tail and spinal cord regeneration in *Xenopus* tadpoles (24).

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