PONTIFICIA ACADEMIA SCIENTIARVM

THE AWARD

OF THE

PIUS XI GOLD MEDAL

2010

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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 25th 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 2010 to

Prof. Patrick Mehlen

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


PIVS · XI · PONTIFEX · MAXIMVS · FVNDATOR
PONTIFICIA · ACADEMIA · SCIENTIARVM
PATRICK MEHLEN
A.D.
MMX

PATRICK MEHLEN

BIOGRAPHICAL DATA

Full Name: Patrick Mehlen

Scientific Discipline: Apoptosis, Cancer and Development

Designation: Professor

Professional Address:
Centre Léon Bérard, Cheney A
28, rue Laënnec
69008 Lyon, France

Date of Birth: 18 February 1968

Place of Birth: Montbéliard, France

Wife and Children: Married to Agnes Bernet-Mehlen; Maxime, Victor, and Lou

Education and Appointment:

2009-date: Co-Director of the Institute for Clinical Science, Centre Léon Bérard

2007-date: Research Director of the laboratory "Apoptosis, Cancer and Development" – CNRS UMR5238, Centre Léon Bérard, Lyon, France. Thematic: "The dependence receptors"

2007-date: Adjunct Professor at the Buck Institute for Age Research, Novato, USA

2004-2006: Research Director of the unit "Apoptosis, Cancer and Development" – CNRS FRE2870, CGMC, Lyon, France. Thematic: "The dependence receptors"

1998-2004: Group leader of the "Apoptosis and Differentiation" Laboratory – CNRS UMR5534, CGMC, Lyon, France. Thematic: "The dependence receptors, switch between cell death and differentiation"

1997-1998: Sabbatical within the Burnham Institute for Medical Research, program on "Aging and Cell Death" – CA, USA. Thematic: "Study on the dependence receptors" – Prof. D.E. Bredesen

Formation:

1989-93: Student of the "Grande Ecole: Ecole Normale Supérieure"

1989-92: "Magistère de Biologie Moléculaire et Cellulaire (LYON)", Equivalent to Master in Biochemistry, Molecular and Cellular Biology

1992-95: Ph. D. Thesis, University Claude Bernard, Lyon, France

2000: "Habilitation à diriger les recherches"

Honors:

Laureate of the Schlumberger Principal Prize 2002

Laureate of the Tartois Prize 2004

Laureate of the Grand Prix Curie-Jeanne Loubaresse 2004

Silver Medal CNRS 2005

Laureate of the Grand Prix EuroCancer 2006

Laureate of the Prix Charles Oberling 2007

Laureate of the Prix Ruban Rose "Grand Prix de la Recherche" 2007

Laureate of the Prix Del Duca de Cancérologie (Académie des Sciences) 2007

Laureate of Grand Prix de l'Innovation "Universal Biotecs", 2009

EMBO Member since 2006

Professor (Adjunct) at the Buck Institute For Age Research, since 2006

Research Evaluation:

President of the ARC committee IV (French Foundation for Cancer Research) (2005-2008)

Vice-President of the INCA libre committee (2008)

Member of "Ligue contre le Cancer" committees (Paris, Rhone-Alpes) (2004-2007)

Member of CNRS (National Center for Scientific Research) ATIP committee (2004–)

Member of ANR (National Agency for Research) blanc committee (2005-2007)

Member of INCA (National Cancer Agency) committee "Libre" (2006)

Editorial Board of Cell Death and Differentiation

Editorial Board of Apoptosis

Referee for various international funding agencies (NSF, EMBO, IARC, Welcome trust, …)

Referee for various international journals (*Nature*, *Science*, *Nature Cell Biology*, *Nature Rev. Cancer*, *Nature Neuroscience*, *EMBO J.*, *J. Cell Biol.*, *Mol. Cell Biol.*, *J. Biol. Chem.*, *Mol. Biol. Cell. J. Neuros.*, *Oncogene*, *BBRC*,…)

Valorisation:

Patent to INPI n° 0011965, September 20, 2000

Patent to US Office, n. 00532-050, February 5, 2006. License cession signed in February 2008 to NTI pharmaceutical and in August 2010 to BioMarin

Patent to US Office, n. 00561-011, February 28, 2006. License cession with Netris Pharma in February 2010

Patent to US Office, n. 61/055.052, May 28, 2008, PCT August 2009

Patent to US Office, n. D26632, May 28, 2008, PCT August 2009

Patent to EU Office, n. EP09305022, January 2009, PCT January 2010

Patent to EU Office, n. EP09161122.8, May 2009

Patent to US Office, n. 0010L0408, April 2010

Co-Founder of the Netris Pharma SAS (June 2008) company which focuses on anti-cancer strategy using the dependence receptor notion

Speciality & Research Field of Interest:

Dependence receptor, Cancer, Development, Apoptosis

Invitation to International Meetings:

50 international conferences as invited speaker since 2000

THE DEPENDENCE RECEPTOR NOTION: APOPTOSIS, FROM CELL BIOLOGY TO TARGETED THERAPY

Since 1998, P. Mehlen's work has been devoted to the development of the dependence receptor notion. P. Mehlen, while working in Dale Bredesen's laboratory in San Diego, proposed that some transmembrane receptors may be active not only in the presence of their ligand as usually believed, but also in their absence. In this latter case, the signaling downstream of these unbound receptors leads to apoptosis. These receptors were consequently named "dependence receptors", as their expression renders the cell's survival dependent on the presence in its environment of its respective ligand (Mehlen *et al.*, 1998, *Nature*). To date, more than 15 dependence receptors have been identified and this functional family includes RET (rearranged during transfection), TrkC, ALK, EPHA4, the netrin-1 receptors DCC (Deleted in Colorectal Cancer) and UNC5H1-4 (Unc-5 homologue 1-4), neogenin, some integrins, and the Sonic Hedgehog receptor Patched (Ptc). P. Mehlen then proposed that the pro-apoptotic activity of these dependence receptors is crucial for the development of the nervous system as a mechanism to "authorize" guidance/migration/localization in settings of ligand presence (Thibert *et al.*, 2003, *Science*; Matsunaga *et al.*, 2004, *Nature Cell Biology*; Tang *et al.*, 2008, *Nature Cell Biology*; Mille *et al.*, 2009, *Nature Cell Biology*). Interestingly, P. Mehlen's group also demonstrated that these dependence receptors represent an important mechanism which limits tumor progression (Mazelin *et al.*, 2004, *Nature*; Mehlen and Puisieux, 2006, *Nature Review Cancer*). The current view is that tumor cells expressing such dependence receptor should undergo apoptosis as soon as primary tumor growth reaches ligand limitation or as soon as tumor cells metastasize in tissues with low ligand content. The demonstration that these dependence receptors were novel types of tumor suppressors was an important discovery in terms of academic research (Prof. Bert Vogelstein interviewed on Mehlen's work by a reporter from the San Francisco Chronicle commented «The

results indicate a fascinating and novel mechanism for (tumor) growth control processes»). However, even more interestingly, recent studies conducted by Mehlen's laboratory propose that this notion of dependence receptor may also lead to appealing anti-cancer strategies. Indeed, Mehlen's group has proposed that in a wide fraction of cancer, the selective advantage that tumors have selected to bypass this dependence for survival on ligand presence is an autocrine secretion of the ligand. Thus, Mehlen's group has shown that in these tumors (e.g., for netrin-1, 47% of lung cancer, 66% of metastatic breast cancer, 40% of neuroblastoma, ect…), disruption of the interaction between the auto-secreted ligand and its dependence receptor reactivates cell death in vitro and is associated with tumor regression in vivo (Fitamant *et al*. 2008, *PNAS*; Delloye-Bourgeois *et al.*, 2009; *JNCI*, Delloye *et al*., 2009, *JEM*; Bouzas *et al.*, 2010, *JCI*, 6 filed Patents since 2006). This has led to the creation of a spin-off company Netris Pharma in June 2008, dedicated to develop candidate drugs which act as interferents to the ligand/dependence receptors interaction. Regarding the first ligand auto-secreted (netrin-1), a candidate drug has been selected and is in pre-clinical development. Interference to two other autosecreted ligands (NT-3 and SHH) is in early development at Netris Pharma. Thus, if the hypothesis is correct, this discovery may lead to clinical phase I study scheduled for 2012. Thus, from a basic cell biology concept, P. Mehlen and his laboratory may, within the next few years, provide new tools to fight against cancer with a wide societal impact.

SELECTED PUBLICATIONS

Mehlen P., Rabizadeh S., Snipas S.J., Assa-Munt N., Salvesen G.S., and D.E. Bredesen (1998) The DCC gene product induces apoptosis by a mechanism requiring receptor proteolysis. *Nature* 395: 801-804.

Bordeaux M.C., Forcet C., Granger L., Corset V., Bidaud C., Billaud M., Bredesen D.E, Edery P. and P. Mehlen (2000). RET as a new dependence receptor: Hirchsprung disease and apoptosis. *EMBO J.* 19: 4056-4063.

Corset V., Tuyen Nguyen-Ba-Charvet K., Forcet C., Moyse E., Chédotal A. and P. Mehlen (2000). Netrin-1 induced growth cone attraction and cAMP production is mediated via interaction with the Adenosine A2b receptor. *Nature* 407: 747-450.

Forcet C., Ye X., Granger L., Corset V., Shin H., Bredesen D.E. and P. Mehlen. (2001) The dependence receptor DCC defines a new pathway for caspase activation. *Proc. Natl. Acad. Sci. USA* 98: 3416-3421.

Llambi F., Causeret F., Bloch-Gallego E., and P. Mehlen (2001). Netrin-1 acts as a survival factor via its receptors UNC5H and DCC. *EMBO J.* 20: 2715-2722.

Forcet C., Stein E., Pays L., Corset V., Llambi F., Tessier-Lavigne M., and P. Mehlen (2002) DCC-dependent MAPK activation is required for netrin-1 mediated axon outgrowth. *Nature* 417: 443-448.

Thiébault K., Mazelin, L., Pays L., Joly, M.O., Scoazec J.Y., Saurin J.C., Romeo G., and P. Mehlen (2003) The netrin-1 receptors UNC5H are putative tumor suppressors controlling cell death commitment. *Proc. Natl. Acad. Sci. USA* 7: 4173-4178.

Thibert C., Teillet M.A., Lapointe F., Mazelin L., LeDouarin, N., and P. Mehlen (2003) Inhibition of neuroepithelial patched-induced apoptosis by sonic hedgehog. *Science* 301: 843-6.

Mehlen P. (2003). A new way to network. *Nature* 424: 381-2.

Matsunaga E., Tauszig-Delamasure S., Monnier P.P, Müeller B., Strittmatter S.M., Mehlen P. and Chédotal A. (2004) RGM and its receptor neogenin regulate neuronal survival. *Nature Cell Biol.* 6: 749-755.

Mazelin L., Bernet A., Bidaud-Bonod C., Pays L., Arnaud S., Gespach C., Bredesen D.E., Scoazec J.Y., and P. Mehlen. (2004) Netrin-1 controls colorectal tumorigenesis by regulating apoptosis. *Nature* 431: 80-84.

Llambi F., Calheiros F., Gozuacik D., Guix C., Pays L., Del Rio G., Kimchi A. and P. Mehlen. (2005) The dependence receptor UNC5H2 mediates apoptosis through DAP kinase. *EMBO J.* 24: 1192-1201.

Mehlen P., Bernet A. (2005). Netrin-1 PIPes up. *Nature Cell Biology* 7: 1052-53.

Furne C., Corset V., Hérincs Z., Cahuzac N., Hueber A.O., and P. Mehlen. (2006). The dependence receptor DCC requires lipid raft localization for cell death signalling. *Proc. Natl. Acad. Sci. USA* 103: 4128-33.

Bredesen D.E., Rao R.V., Mehlen P. (2006) Cell death in the nervous system. *Nature* 443: 796-802.

Mehlen P., Puisieux A. (2006). Metastasis: a question of life or death. *Nature Rev. Cancer* 6: 449-458.

Tauszig-Delamasure S., Yu L.Y., Cabrera J.R., Bouzas J., Mermet-Bouvier C., Guix C., Bordeaux M.C., Arumae U., and P. Mehlen (2007). The TrkC receptor induces apoptosis, when the dependence receptor notion meets the neurotrophin paradigm. *Proc. Natl. Acad. Sci. USA* 104: 13361-6.

Fitamant J., Guenebeaud C., Coissieux M.M, Guix C., Treilleux I., Scoazec J.Y., Bachelot T., Bernet A., and P. Mehlen (2008). Netrin-1 expression confers a selective advantage for tumor cell survival in metastatic breast cancer. *Proc. Natl. Acad. Sci. USA* 105: 4850-5.

Tang X., Jang S.W., Okada M., Chan C.B., Feng Y., Luo S.W., Hong Y., Liu Y., Rama N., Xiong W.C., Mehlen P. and K. Ye (2008). Netrin-1 Mediates Neuronal Survival Through PIKE-L Interaction With the Dependence Receptor UNC5B. *Nature Cell Biology* 10: 698-706.

Furne C., Rama N., Corset V., Chédotal A. and P. Mehlen (2008). Netrin-1 is a survival factor during commissural neuron navigation. *Proc. Natl. Acad. Sci. USA* 105: 14465-70.

Delloye-Bourgeois C., Brambilla E., Coissieux M.M., Guenebeaud C, Pedeux R., Firlej V., Cabon F., Brambilla C., Mehlen P. and A. Bernet (2008) Interference with Netrin-1 and Tumor Cell Death in Non-Small Cell Lung Cancer. *J. Natl. Cancer Inst.* 101: 237-247.

Delloye-Bourgeois C., Fitamant J., Paradisi A., Cappellen D., Douc-Rasy S., Raquin M.A., Stupack D., Nakagawara A., Combaret V., Puisieux A., Couanet-Valteau D., Bénard J., Bernet A. and P. Mehlen (2009b). Netrin-1 acts as a survival factor for aggressive neuroblastoma. *J. Exp. Medicine* 206: 833-847.

Castets M., Coissieux M.M., Delloye-Bourgeois C., Bernard L., Delcros J.G., Bernet A., Laudet V. and P. Mehlen (2009). Inhibition of endothelial cell apoptosis by netrin-1 during angiogenesis. *Dev. Cell* 16: 614-620.

Mille F., Thibert C., Fombonne J., Rama N., Guix C., Hayashi H., Corset V., Reed J.C., and P. Mehlen (2009). The Patched dependence receptor triggers apoptosis through a DRAL-caspase-9 complex. *Nature Cell Biology* 11: 739-46.

Paradisi A., Maisse C., Coissieux M.M., Gadot N., Lépinasse F., Delloye-Bourgeois C., Delcros J.G., Svrcek M., Neufert C., Fléjou J.F., Scoazec J.Y. and P. Mehlen (2009). Netrin-1 up-regulation in inflammatory bowel diseases is required for colorectal cancer progression. *Proc. Natl. Acad. Sci. USA* 106: 17146-51.

Bouzas-Rodriguez J., Ruben Cabrera J., Delloye-Bourgeois C., Ichim G., Delcros J.G., Raquin M.A., Rousseau R., Combaret V., Bénard J., Tauszig-Delamasure, S., and P. Mehlen (2010). NT-3 production promotes neuroblastoma cell survival by inhibiting TrkC-induced apoptosis. *J. Clin. Investigation*, 120(3): 850-8.

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