


The Giovanni  
Armenise-Harvard Foundation

CAREER DEVELOPMENT AWARDEES

	<p><i>Nico Mitro, Ph.D.</i></p>
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<b>Title</b>	<b>Giovanni Armenise-Harvard Career Development Awardee</b>
<b>Office</b>	<i>Via Balzaretti 9, 20133 Milano, Italy</i>
<b>Tel &amp; Fax</b>	<i>Phone: 00390250318344, Fax: 00390250318391</i>
<b>Email</b>	<i>nico.mitro@unimi.it</i>
<b>Home Page</b>	<i><a href="http://users.unimi.it/DPS/person.php?id=168">http://users.unimi.it/DPS/person.php?id=168</a></i>
<b>Host Institute</b>	<i><a href="http://users.unimi.it/DPS/">http://users.unimi.it/DPS/</a></i>

<b>Laurea</b>	<i>University of Milano, Milano, Italy. 02/05/2001</i>
<b>Ph.D</b>	<i>University of Siena, Siena, Italy. 01/31/2006</i>
<b>Postdoc</b>	<i>Genomics Institute of the Novartis Research Foundation, San Diego, California, USA. From April 2005 to September 2006. The Scripps Research Institute, La Jolla, California, USA. From September 2006 to July 2008.</i>
<b>Previous work experience</b>	<i>Dr. Mitro research career started describing a coordinated regulation of cholesterol and glucose metabolism by bile acids and identifying a possible target for new hypocholesterolemic drugs. In collaboration with other groups, dr. Mitro worked on the synthesis, biological evaluation, and molecular modeling of new dual ligand of the PPAR (Peroxisome Proliferator-Activated Receptor) <math>\alpha</math> and <math>\gamma</math>, and he also showed that some natural molecule decrease transcription, expression, secretion and activity of the MMP-9. In April 2005, dr. Mitro joined the laboratory of dr. Enrique Saez at the Genomics Institute of the Novartis Research Foundation, and then moved with his group to The Scripps Research Institute, in La Jolla, CA, USA. In this lab dr. Mitro familiarized with cutting-edge genomic screening tools. His studies investigated the role of the Liver X receptors (LXR) in glucose metabolism. In particular, he discovered and described a new mechanism whereby glucose determines its own fate: he showed that glucose binds and stimulates the transcriptional activity of the nuclear receptor LXR. Dr. Mitro proposed LXR as hepatic glucose sensor. Moreover in collaboration with other colleagues dr. Mitro contributed to elucidate the anti-diabetic properties of the synthetic LXR ligand GW3965. In collaboration with dr. Tontonoz group he identified a natural small molecule (harmine) that despite inducing adipocytes differentiation, has anti-diabetic effects.</i>
<b>Association memberships</b>	<i>From 2001 member of of the Italian Society for the Study of Atherosclerosis (SISA) From 2001 member of the National Association of Italian Biotechnologist (ANBI) From 2004 member of the Italian Society of Biochemistry (SIB)</i>

<b>Research Interests</b>	<i>Atherosclerosis and cardiovascular disease are the major causes of mortality in patients with diabetes. Coronary heart disease and stroke are more common, and occur at an earlier age, in diabetic patients than in the general population, regardless of serum cholesterol levels.. Yet, the cellular and molecular mechanisms that underlie the potentiating influence of diabetes on the development and progression of atherosclerosis</i>
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	<p>remain poorly understood. Liver X receptors (LXRs) are ligand activated transcription factors that belong to the nuclear receptor family. The LXRs serve as cholesterol sensors that prevent excessive intracellular accumulation of cholesterol. Oxysterols (oxidized forms of cholesterol) activate the LXRs and they induce expression of a battery of genes aimed at eliminating detrimental concentrations of cholesterol. Besides modulating cholesterol metabolism, the LXRs also control key genes involved in fatty acid and glucose metabolism. Because oxysterols are the best characterized LXR ligands, and the rodent diet is practically devoid of cholesterol, to explore the dietary influences that modulate hepatic LXR function we asked whether LXR activity could be regulated by other nutrients such as glucose. We recently demonstrated that glucose regulates LXR activity at physiological concentrations expected in the liver, and that it induces expression of LXR target genes with similar efficacy as oxysterols. Our data outlines a role for LXR in a carbohydrate signaling pathway. The LXRs are the first nuclear receptors described to integrate metabolic signals: glucose and oxysterol can bind the LXRs simultaneously and dual occupancy increases receptor activity. Since LXRs are unique transcription factors that can sense both glucose and oxysterols, they may represent a transcriptional link between diabetes and atherosclerosis. Our lab is using a mutational approach to dissect LXR signaling and test the hypothesis that LXRs behave as dual glucose-oxysterol sensors in vivo, a prelude to assessing whether they connect these two diseases.</p> <p>A second research line in the lab aim to understand the mechanisms that control mitochondrial biogenesis to discover targets for the design of new pharmacological approaches restoring a correct oxidative metabolism to apply in mitochondrial diseases (diabetes, cancer, etc.).</p> <p>In summary, the general research goal of our laboratory is to understand how diet influences gene expression, and the genetic regulation of energy balance.</p>
<p><b>Selected Publications</b></p>	<ol style="list-style-type: none"> <li>1. Sironi L.#, Mitro N.#, Cimino M., Gelosa P., Guerrini U., Tremoli E. and Saez E. "Treatment with LXR agonists after focal cerebral ischemia prevents brain damage." <i>FEBS Letters</i>. 2008 Sep 9. #SL and NM contributed equally to this paper.</li> <li>2. C. Wu, D.L. Delano, N. Mitro, S.V. Su, J. Janes, P. McClurg, S. Batalov, G.L. Welch, J. Zhang, A. P. Orth, J.R. Walker, R.J. Glynn, M. P. Cooke, J.S. Takahashi, K. Shimomura, A. Kohsaka, J. Bass, E. Saez, T. Wiltshire and A.I. Su. "Gene set enrichment in eQTL data identifies novel annotations and pathway regulators". <i>PLoS Genetics</i>, 2008 9; 4(5): e1000070.</li> <li>3. S.R. Commerford, L. Vargas, S.E. Dorfman, P.A. Mak, N. Mitro, E.C. Rocheford, X. Li, P. Kennedy, T.L. Mullarkey, and E. Saez. "Dissection of the Anti-diabetic Effect of Liver X Receptor Ligands". <i>Molecular Endocrinology</i>, 2007, 21(12): 3002-1.</li> <li>4. V. Molteni, X. Li, J. Nabakka, F. Liang, J. Wityak, A. Koder, L. Vargas, R. Romeo, N. Mitro, P.A. Mak, H.M. Seidel, J.A. Haslam, T. Tunland, T.A. Spalding, A. Brock, M. Bradley, A. Castrillo, P. Tontonoz and E. Saez. "N-Acylthiadiazolines, a new class of Liver X Receptor agonists with selectivity for LXR<math>\beta</math>". <i>The Journal of Medicinal Chemistry</i>, 2007 50(17): 4255-9.</li> <li>5. N. Mitro, C. Godio, E. De Fabiani, E. Scotti, A. Galmozzi, F. Gilardi, D. Caruso, A. B. Vigil Chacon, and M. Crestani. "Analysis of nuclear factors dynamically recruited to cholesterol 7<math>\alpha</math>-hydroxylase gene reveals a target for treatment of hypercholesterolemia". <i>Hepatology</i>, 2007; 46(3): 885-97.</li> <li>6. M. Bertolotti, C. Gabbi, C. Anzivino, M. Crestani, N. Mitro, M. Del Puppo, C. Godio, E. De Fabiani, D. Macchioni, L. Carulli, A. Rossi, M. Ricchi, P. Loria, N. Carulli. "Age-related changes in bile acid synthesis and hepatic nuclear receptor expression". <i>European Journal of Clinical Investigation</i>, 2007; 37(6): 501-8.</li> <li>7. Waki H., Park K.W., Mitro N., Pei L., Damoiseaux R., Wilpitz D.C., Reue K., Saez E. and Tontonoz P. "The small molecule harmine is an antidiabetic cell-type-specific regulator of PPAR<math>\gamma</math> expression". <i>Cell Metabolism</i>, 2007 May; 5(5): 357-70.</li> <li>8. Mitro N., Vargas L., Romeo R., Koder A. and Saez E. "T0901317 is a potent PXR ligand: Implications for the biology ascribed to LXR". <i>FEBS Letters</i>, 2007; 581(9): 1721-6.</li> <li>9. G. Pochetti, C. Godio, N. Mitro, D. Caruso, A. Galmozzi, S. Scurati, F. Loiodice, G. Fracchiolla, P. Tortorella, A. Laghezza, A. Lavecchia, E. Novellino, F. Mazza, and M. Crestani "Insights into the mechanism of partial agonism: crystal structures of the peroxisome proliferator-activated receptor gamma ligand-binding domain in the complex with two enantiomeric ligands" <i>The Journal of Biological Chemistry</i>, 2007; 282(23): 17314-24.</li> <li>10. N. Mitro, P. A. Mak, L. Vargas, C. Godio, E. Hampton, V. Molteni, A. Kreuzsch &amp; E. Saez. "The nuclear</li> </ol>

receptor LXR is a glucose sensor". *Nature*, 2007; 445(7124): 219-223.

11. Dell'Agli M., Fagnani R., Mitro N., Scurati S., Masciadri M., Mussoni L., Galli G.V., Bosisio E., Crestani M., De Fabiani E., Tremoli E., Caruso D. "Minor components of olive oil modulate proatherogenic adhesion molecules involved in endothelial activation." *The Journal of Agricultural and Food Chemistry*, 2006; 54(9): 3259-64.

12. M. Bertolotti, C. Gabbi, C. Anzivino, N. Mitro, C. Godio, E. De Fabiani, M. Crestani, M. Del Puppo, M. Ricchi, L. Carulli, A. Rossi, P. Loria, and N. Carulli. "Decreased hepatic expression of PPAR- $\gamma$  coactivator-1 in cholesterol cholelithiasis". *European Journal of Clinical Investigation*, 2006; 36(3): 170-5.

13. Pinelli A., Godio C., Laghezza A., Mitro N., Fracchiolla G., Tortorella V., Lavecchia A., Novellino E., Fruchart J.C., Staels B., Crestani M., and Loiodice F. "Synthesis, biological evaluation, and molecular modeling investigation of new chiral fibrates with PPAR $\alpha$  and PPAR $\gamma$  agonist activity". *The Journal of Medicinal Chemistry*, 2005; 48(17):5509-19.

14. Caruso D., Crestani M., Mitro N., Da Riva L., Mozzi R., Sarpau S., Merlotti C., and Franzini C. "High pressure liquid chromatography and electrospray ionization mass spectrometry are advantageously integrated into a two-levels approach to detection and identification of haemoglobin variants". *Clinical and Laboratory Haematology*, 2005; 27(2):111-9.

15. M.L. Trincavelli, M. Marroni, D. Tuscano, S. Ceruti, A. Mazzola, N. Mitro, M.P. Abbracchio and C. Martini. "Regulation of A2b adenosine receptor functioning by tumor necrosis factor alpha in human astroglial cells". *The Journal of Neurochemistry*, 2004; 91(5):1180-90.

16. D. Caruso, M. Crestani, L. Da Riva, N. Mitro, F. Giavarini, R. Mozzi and C. Franzini. "Mass spectrometry and DNA sequencing are complementary techniques for the characterisation of haemoglobin variants: the example of haemoglobin J-Oxford". *Haematologica*, 2004; 89: 608-609. (I.F. 4.192)

17. E. De Fabiani#, N. Mitro#, F. Gilardi, D. Caruso, G. Galli and M. Crestani. "Coordinated control of cholesterol catabolism to bile acids and of gluconeogenesis via a novel mechanism of transcription regulation linked to the fasted-to-fed cycle". *The Journal of Biological Chemistry*, 2003, 278(40): 39124-39132. #EDF and NM contributed equally to this paper.

18. S. Bellosta, M. Dell'Agli, M. Canavesi, N. Mitro, M. Monetti, M. Crestani, L. Verotta, N. Fuzzati, F. Bernini and E. Bosisio. "Inhibition of metalloproteinase-9 activity and gene expression by polyphenolic compounds isolated from the bark of *Tristaniopsis calobuxus* (Myrtaceae)". *Cellular and Molecular Life Sciences*, 2003, 60(7): 1440-1448.

19. E. De Fabiani, N. Mitro, A.C. Anzulovich, A. Pinelli, G. Galli and M. Crestani. "The negative effects of bile acids and tumor necrosis factor- $\alpha$  on the transcription of cholesterol 7 $\alpha$ -hydroxylase gene (CYP7A1) converge to hepatic nuclear factor-4". *The Journal of Biological Chemistry*, 2001, 276(33): 30708-30716.

#### REVIEWS

20. Mitro N., Gilardi F., Godio C., Scotti E., De Fabiani E., Caruso D., and Crestani M. "Bile acids and gene regulation: from nuclear receptors to chromatin." *Frontiers Bioscience*, 2008, 1;13:6276-88.

21. F. Gilardi, N. Mitro, C. Godio, E. Scotti, D. Caruso, M. Crestani, E. De Fabiani "The pharmacological exploitation of cholesterol 7 $\alpha$ -hydroxylase, the key enzyme in bile acid synthesis: from binding resins to chromatin remodelling to reduce plasma cholesterol" *Pharmacology and Therapeutics*, 2007, 116(3): 449-72.

22. E. Scotti, F. Gilardi, C. Godio, E. Gers, J. Krneta, N. Mitro, E. De Fabiani, D. Caruso, M. Crestani "Bile acids and their signaling pathways: eclectic regulators of diverse cellular functions" *Cellular and Molecular Life Sciences*, 2007, 64(19-20): 2477-91.

23. M. Crestani, E. De Fabiani, D. Caruso, N. Mitro, F. Gilardi, A.B. Vigil Chacon, R. Patelli C. Godio and G. Galli "LXR and HNF-4: key regulators in reverse cholesterol transport" *Biochemical Society Transactions*, 2004, 32: 92-96.

24. M. Crestani, N. Mitro and E. De Fabiani. "Nuclear receptors: from gene transcription to the control of cellular metabolism" *European Journal of Lipid Science and Technology*, 2004, 106:432-450.

25. E. De Fabiani, N. Mitro, C. Godio, F. Gilardi, D. Caruso, and M. Crestani "Bile acid signaling to the nucleus: finding new connections in the transcriptional regulation of metabolic pathways" *Biochimie*, 2004; 86(11): 771-8.

Laboratory Members	<i>Gaia Cermenati Ph.D., position: Postdoc</i> <i>Alice Molteni, position: under-graduate student</i>

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