Dimitra J Mitsiou

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Curriculum Vitae

Education

1996: PhD thesis, Department of Biology, Athens University.
1989: Diploma in Biology, Department of Biology, Athens University.

Appointments - Research activity

2009-present: Research Assistant Professor (Researcher C) at the Molecular Endocrinology Programme, IBMCB-NHRF [IBMCB is the result of the merger of the Institute of Biological Research and Biotechnology (IBRB) and the Institute of Organic and Pharmaceutical Chemistry (IOPC) of NHRF in 2012].
2006-2009: Research Lecturer (Researcher D) at the Molecular Endocrinology Programme, IBRB-NHRF.
2001-2006: Post doctoral fellow at the Molecular Endocrinology Programme, IBRB-NHRF.
1997-2001: Post doctoral fellow at the Department of Molecular Biology (Prof. H.G. Stunnenberg) initially at the Katholieke University of Nijmegen (KUN) and then at the Nijmegen Center for Molecular Life Sciences (NCMLS), Radboud Universiteit Nijmegen, The Netherlands.
1995-1996: Post doctoral fellow at the Molecular Endocrinology Programme, IBRB-NHRF.
1990-1995: Predoctoral fellow at the Molecular Endocrinology Programme, IBRB-NHRF (PhD thesis supervisor: Dr. MN Alexis, thesis title: 'Glucocorticoid receptor interaction with heat shock proteins').
1988-1989: Diploma thesis (research) at the Molecular Endocrinology Programme, IBRB-NHRF (thesis supervisor: Dr. MN Alexis, thesis title: 'Glucocorticoid receptor structure').

Honours, awards, distinctions

2001-2002: EU Marie Curie-TMR-Return individual postdoctoral fellowship (HPMI-CT-2000-00904), in the context of Training and Mobility of Researchers (TMR) Work Programme, for research at the Molecular Endocrinology Programme, IBRB-NHRF.
1998-2000: EU Marie Curie-TMR individual postdoctoral fellowship (ERB-FMBI-CT97-2728), in the context of Training and Mobility of Researchers (TMR) Work Programme, for

research at the Department of Molecular Biology, Katholieke University of Nijmegen, The Netherlands.

1990-1995: Individual predoctoral fellowship from NHRF, for PhD research at the Molecular Endocrinology Programme, IBRB-NHRF.

Research Achievements

Research performed during PhD studies and postdoctoral work focused on the:

- subunit composition of glucocorticoid receptor (GR) complex.
- role of heat shock proteins (HSPs) on GR structure and function.
- transcriptional regulation mediated by nuclear hormone receptors (GR, ER, RAR).
- cell-type specific roles of general transcription factors (TBP and TFIIA) and the identification of a novel transcription complex (TAC), a TBP-sans TAFs complex containing the unprocessed TFIIA$\alpha\beta$ precursor and the TFIIAγ subunit that is involved in transcriptional regulation in embryonal carcinoma (EC) cells.
- processing of TFIIA$\alpha\beta$ and its identification as a substrate of taspase 1, the protease that cleaves the trithorax group mixed-lineage leukemia protein.
- transcriptional coactivators (p300) and protein modifications (acetylation, ubiquitination) that play important roles in transcription.
- phytoestrogens acting as estrogen receptor beta (ERβ) specific ligands (deoxybenzoins, intermediates in the synthesis of isoflavones).

Research performed during her appointment as Lecturer and Research Assistant Professor focused on the:

- role of estrogen receptor β (ERβ) on breast cancer (BC), particularly on a) the effects of ERβ1 and ERβ2 isoforms on the development of drug (antiestrogens and retinoids) resistance and the regulation of gene expression in BC cells and b) the evaluation of ERβ1 and ERβ2 as prognostic markers of BC.
- production and characterization of antibodies against GR and ERα and ERβ isoforms that are valuable tools for studying GR and ER signalling pathways.
- development of a bacterial sensor, comprising the LBD of the human estrogen receptor α (ERα) and the very sensitive reporter enzyme thymidylate synthase (TS), that is appropriate for screening applications of potentially therapeutic compounds.
- global crosstalk of glucocorticoid receptor (GR) and nuclear factor kappa-b (NFKB) on chromatin.

Recent Research Highlights and Current Research Interests

Recent Research Highlights

- production and characterization of antibodies against GR and ERα and ERβ isoforms that are valuable tools for studying GR and ER signalling pathways (Chantzi et al. 2011; Rao et al. 2011). Two of these antibodies were put on the market by Diagenode SA (http://www.diagenode.com).

- global interaction of glucocorticoid receptor (GR) and nuclear factor kappa-b (NFKB) on chromatin, using state-of-the-art technologies (ChIP-sequencing, in collaboration with Prof. Stunnenberg, Rao et al. 2011), that provides a novel genome-wide footprint of GR and NFKB crosstalk and substantially contribute to the understanding of the networks underlying the glucocorticoid and inflammatory signaling pathways. These observations open up new research directions and similar approaches are now applied in the current research projects.

Current Research Interests

Current research aims at unravelling the role of glucocorticoid and estrogen receptors (GR and ER, respectively) in the context of health and disease. The main focus is on the regulatory networks underlying GR and ER signalling pathways in diseases with emphasis on cancer, particularly breast cancer (BC), and on endocrine-related chronic diseases such as osteoporosis. Global analysis of GR and ER targets using state-of-the art genome-wide approaches (as already reported for the GR and NFKB crosstalk) is expected to contribute to the identification of new targets and the development of targeted therapeutic approaches. More specifically current interests focus on the:

- putative role of GR on the NFKB-mediated development of resistance of breast cancer cells to antiestrogens (tamoxifen) and the identification of selective glucocorticoids (DGCs, dissociated glucocorticoids; non-steroid compounds that mediate repression of NFKB activity but not transactivation of GR direct targets) able to restore sensitivity. Putative DGCs will be developed by IBMCB researchers and will be tested for their potential to restore tamoxifen sensitivity in resistant BC cells. Global transcriptome profiles from resistant cells treated with a selected lead alone and in combination with tamoxifen will reveal the mechanism(s) of DGC action and the molecular networks involved in restoration of tamoxifen sensitivity.

  Research Funding Programme KRIPIS: Project STHENOS (2012-2015): Targeted therapeutic approaches against degenerative diseases with emphasis on cancer and aging. Participants: all IBCMB–NHRF researchers.
- development of mutant PIK3CA specific inhibitors acting as anticancer drugs and identification of the determinants of BC resistance to antiestrogens. Mutations in the catalytic p110α subunit of PI3K leads to its aberrant activation and are often linked to the development of antiestrogen resistance of BC cells. Putative inhibitors specific for the mutant PI3K were/are developed from the project consortium and are evaluated, either alone or in combination with antiestrogens (tamoxifen, ICI) and EGFR/HER2 inhibitors (lapatinib), for their effect on proliferation, viability and invasiveness of ERα positive BC bearing mutations of PI3K in the presence or absence of PTEN (PI3K inhibitor). In parallel, identification of the global trasncriptome profile of these cells treated with the lead compound alone or in combination with tamoxifen or lapatinib will reveal the gene networks underlying the mechanisms of combinatorial therapies and will identify putative new markers associated with resistance to these therapies.

  Research Funding Program COOPERATION: project 09ΣΥΝ-11-675 (2010-2014): 'PIK3CA Oncogenic Mutations in Breast and Colon Cancers: Development of Targeted Anticancer

Drugs and Diagnostics'. Participants: Genetics Division/BRFAA, Signal-mediated Gene Expression-Molecular Endocrinology-Metabolic Engineering & Bioinformatics ProgrammesIBCMRB–NHRF, BRI-FORTH, ProActina SA, Pharmathen Pharmaceuticals, Bioiatriki.

- identification/development of SERMS (natural or synthetic products) for prevention/treatment of postmenopausal symptoms such as osteoporosis and hypercholisterolemia. Compounds of natural or synthetic origin will be evaluated for their ability to promote osteoblastogenesis and inhibit osteoclastogenesis in vitro, to act as antiestrogens in breast and uterus (anticancer activity) and to have no effect on differentiation of normal mammary epithelial cells. Lead compounds will be selected and evaluated in vivo for the potential to prevent hypercholesterolemia and osteoporosis in the ovariectomized mouse. In parallel, global transcriptome profiles of the lead compound(s) in in vitro models of osteblastogenesis and osteoclastogenesis will unravel the mechanisms involved in prevention of osteoporosis. Mapping of the global chromatin binding and transcriptome profiles of ERα and/or ERβ from normal mammary epithelial cells treated with the lead compound(s) will provide the 'binding and gene signatures' for safe SERM action.

  Research Funding Program COOPERATION: Project 09 ΣΥΝ-11-1076 (2011-2015): 'Development of natural products and analogues for osteoporosis prevention: transcriptomic, proteomic and metabolomic approaches'. Participants: Dept of Pharmacognosy & Natural Products Chemistry-School of Pharmacy-Univ. of Athens, Molecular Endocrinology Programme-IBCMRB-NHRF, Dept of Surgery-Musculoskeletal System Research Lab-School of Medicine-Univ. of Athens, Lavipharm SA.

  Research Funding Program THALES: Project 80038 (2012-15): 'Development of new selective estrogen receptor modulators for preventing menopause consequences (SERMENCO)'. Participants: Dept of Pharmacognosy & Natural Products Chemistry-School of Pharmacy-Univ. of Athens, Molecular Endocrinology Programme-IBCMRB-NHRF, Dept of Chemistry-Agricultural Univ. of Athens.
- prognostic and therapeutic significance of ERβ in Triple Negative Breast Cancer (TNBC). Global chromatin binding and transcriptome profiles of ERβ1 and ERβ2 isoforms of ERβ from WT and BRCA1-mutant TNBC cells treated with estrogen and/or tamoxifen will reveal the molecular footprint of ERβ1 and ERβ2 action in these cells.

  Research Funding Program THALES: Project 85355 (2012-15): 'Molecular sub-typing of Triple Negative Breast Cancer (TNBC)'. Participants: Dept of Medical Oncology-School of Medicine-Univ. of Thessaloniki, Molecular Diagnostics Laboratory-National Centre of Scientific Research 'Demokritos', Molecular Endocrinology Programme-IBCMRB-NHRF and Dept of Basic Medical Sciences-School of Medicine-Univ. of Athens.

Funding

2013-2015: Research Funding Programme KRIPIS (2012-2015): Targeted therapeutic approaches against degenerative diseases with emphasis on cancer and aging (STHENOS).

2012-2015: Research Funding Program THALIS: Project 80038 (2012-15): Development of new selective estrogen receptor modulators for preventing menopause consequences (SERMENCO).

2012-2015: Research Funding Program THALIS: Project 85355 (2012-15): Molecular sub-typing of Triple Negative Breast Cancer (TNBC).

2011-2014: 09ΣΥΝ-11-1076 (2011-2014): National action 'Cooperation' – Sub-action I: Medium & Small Scale Cooperative Projects: 'Development of natural products and analogues for osteoporosis prevention: transcriptomic, proteomic and metabolomic approaches

2010-2014: 09ΣΥΝ-11-675 (2010-2014): National action 'Cooperation' – Sub-action II: Large Scale Cooperative Projects: 'PIK3CA Oncogenic Mutations in Breast and Colon Cancers: Development of Targeted Anticancer Drugs and Diagnostics'.

2006-2009: General Secretariat for Research and Technology (GSRT) PENED03-ΕΔ644 project.

2004-2008: EU MTKD-CT-2004-509836 project, in the context of Marie Curie Development Host-Transfer of Knowledge Programme.

2002-2007: Funding in the context of the Marie Curie Development Host Programme (HPMD-CT-2001-00116 project) and the GSRT E!3060-SERMS project for research at the Molecular Endocrinology Programme, IBRB-NHRF.

2001-2002: EU Marie Curie-TMR-Return individual postdoctoral fellowship (HPMI-CT-2000-00904), in the context of Training and Mobility of Researchers (TMR) Work Programme, for research at the Molecular Endocrinology Programme, IBRB-NHRF.

2000-2001: Postdoctoral fellowship from the Radboud Universiteit Nijmegen, Department of Molecular Biology/Nijmegen Center for Molecular Life Sciences (NCMLS), The Netherlands.

1998-2000: EU Marie Curie-TMR individual postdoctoral fellowship (ERB-FMBI-CT97-2728), in the context of Training and Mobility of Researchers (TMR) Work Programme, for research at the Department of Molecular Biology, Katholieke University of Nijmegen, The Netherlands.

1997: Postdoctoral fellowship, in the context of ERB-FMRX-CT96-0064 project (EU-TMR Network), from the Katholieke University of Nijmegen, Department of Molecular Biology, The Netherlands.

1996: Postdoctoral fellowship, in the context of the GSRT PENED.1995 Programme, from the Molecular Endocrinology Programme, IBRB-NHRF.

1990-1995: Individual predoctoral fellowship from NHRF, for PhD research at the Molecular Endocrinology Programme, IBRB-NHRF.

Publications in international referred journals

1. Dhimolea E, Tiniakos DG, Chantzi NI, Goutas N, Vassilaros SD, Mitsiou DJ, Alexis MN. (2015). Estrogen receptors β1 and β2 are associated with distinct responses of estrogen receptor α-positive breast carcinoma to adjuvant endocrine therapy. Cancer Lett. 358, 37-42.

2. Chantzi NI, Palaiologou M, Stylianidou A, Goutas N, Vassilaros S, Kourea HP, Dhimolea E, Mitsiou DJ, Tiniakos DG, Alexis MN. (2014). Estrogen receptor β2 is inversely correlated with Ki-67

in hyperplastic and noninvasive neoplastic breast lesions. J. Cancer Res. Clin. Oncol. 140(6), 1057-1066.

3. Panagiotidou E, Zerva S, Mitsiou DJ, Alexis MN, Kitraki E. (2014). Perinatal exposure to low dose bisphenol A affects the neuroendocrine stress response in rats. J. Endocrinol., 220(3), 207-218.

4. Chantzi NI, Tiniakos DG, Palaiologou M, Goutas N, Filippidis T, Vassilaros SD, Dhimolea E, Mitsiou DJ, Alexis MN (2013). Estrogen receptor beta 2 is associated with poor prognosis in estrogen receptor alpha-negative breast carcinoma. J. Cancer Res. Clin. Oncol. 139(9), 1489-1498.

5. Rao NA, McCalman MT, Moulos P, Francoijs KJ, Chatziioannou A, Kolisis FN, Alexis MN, Mitsiou DJ, Stunnenberg HG (2011). Coactivation of GR and NFKB alters the repertoire of their binding sites and target genes. Genome Res. 21(9), 1404-1416.

6. Chantzi NI, Meligova AK, Dhimolea E, Petrou CC, Mitsiou DJ, Magafa V, Pechtelidou A, Florentin I, Kitraki E, Cordopatis P, Tiniakos DG, Alexis MN (2011). Insights into ectopic estrogen receptor expression, nucleocytoplasmic distribution and interaction with chromatin obtained with new antibodies to estrogen receptor α and β. Steroids 76(10-11), 974-985.

7. Skretas G, Meligova AK, Villalonga-Barber C, Mitsiou DJ, Alexis MN, Micha-Screttas M, Steele BR, Screttas CG, Wood DW (2007). Engineered chimeric enzymes as tools for drug discovery: generating reliable bacterial screens for the detection, discovery and assessment of estrogen receptor modulators. J. Am. Chem. Soc. 129, 8443-8457.

8. Høiby T, Zhou H, Mitsiou DJ, Stunnenberg HG (2007). A facelift for the general transcription factor TFIIA. Biochim. Biophys. Acta 1769, 429-436.

9. Zhou H, Spicuglia S, Hsieh JJ, Mitsiou DJ, Høiby T, Veenstra GJ, Korsmeyer SJ, Stunnenberg HG (2006). Uncleaved TFIIA is a substrate for taspase1 and active in transcription. Mol. Cell. Biol. 26, 2728-2735.

10. Mitsiou DJ, Florentin I, Baki L, Georgakopoulos A, Alexis MN (2005). Pronounced enhancement of glucocorticoid-induced gene expression following severe heat shock of heat conditioned cells hints to intricate cell survival tactics. J. Steroid Biochem. Mol. Biol. 94, 209-217.

11. Siriani D, Mitsiou DJ, Alexis MN (2005). Heat-induced degradation of overexpressed glucocorticoid receptor. Separate protective roles of hsp90 and hsp70. J. Steroid Biochem. Mol. Biol. 94, 93-101.

12. Høiby T, Mitsiou DJ, Zhou H, Erdjument-Bromage H, Tempst P, Stunnenberg HG (2004). Cleavage and proteasome-mediated degradation of the basal transcription factor TFIIA. EMBO J. 23, 3083-3091.

13. Fokialakis N, Lambrinidis G, Mitsiou DJ, Aligiannis N, Mitakou S, Skaltsounis AL, Pratsinis H, Mikros E, Alexis MN (2004). A New Class of Phytoestrogens: Evaluation of the Estrogenic Activity of deoxybenzoins. Chemistry and Biology 11, 397-406.

14. Mitsiou DJ, Stunnenberg HG (2003). p300 is involved in formation of the TBP-TFIIA-containing basal transcription complex, TAC. EMBO J. 22, 4501-4511.

15. Siriani D, Mitsiou DJ, Alexis MN (2003). Overexpressed glucocorticoid geceptor negatively regulates gene expression under normal growth conditions. J. Steroid Biochem. Mol. Biol. 84, 171-180.

16. Mitsiou DJ, Siriani D, Katsanou F, Florentin I, Georgakopoulos A, Alexis MN (2003). Maintenance of glucocorticoid receptor function following severe heat-shock of heat-conditioned cells. Mol. Cell. Endocrinol. 201, 97-108.

17. Mitsiou DJ, Stunnenberg HG (2000). TAC, a TBP-sans TAFs complex containing the unprocessed TFIIA$\alpha\beta$ precursor and the TFIIAγ subunit. Molecular Cell 6, 527-537.

18. Mitsiou DJ, Alexis MN (1995). Temporary loss of glucocorticoid receptor-mediated regulation of gene expression in heat-shocked cells. FEBS Letters 362, 309-315.

19. Alexis MN, Mavridou I, Mitsiou DJ (1992). Subunit composition of the untransformed glucocorticoid receptor in the cytosol and in the cell. Eur. J. Biochem. 204, 75-84.

Team members

Michael N. Alexis, PhD	Research Professor (Head)
Dimitra J. Mitsiou, PhD	Research Assistant Professor
Jelena Nestorov	Visiting Researcher
Athina Boulaka	Postdoctoral fellow
Eleni Kouverianou	Postdoctoral fellow
Aggeliki K. Meligova	Postdoctoral fellow
Vassilis Mersinias	Postdoctoral fellow
Dimitra Siakouli	PhD student
Marion Glava	Postgraduate student
Vassilis Ritsos	Graduate student
Chrysoula Tsirigoti	Graduate student