

CURRICULUM VITAE

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Dr. George Simos

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Education

Bachelor of Science, Biochemistry, Sussex University, U.K., 1981

Diploma of Chemistry, University of Thessaloniki, Greece, 1984

Doctorate Diploma (PhD) in Biochemistry, University of Thessaloniki, Greece, 1990

Professional positions

1990-1994: Post-doctoral fellow, Cell Biology Program, EMBL, Heidelberg

1995-2000: Wiss. Assistent (C1), Biochemie-Zentrum Heidelberg, Faculty of Medicine, University of Heidelberg

2001-2006: Assistant Professor, School of Medicine, University of Thessaly,

Since Jan 2007: Associate Professor of Biochemistry

Since Mar 2009: Director of the Department of Biochemistry, School of Medicine, University of Thessaly

Research experience & achievements

I studied Biochemistry at the University of Sussex, England and Chemistry at the Univ. of Thessaloniki, Greece. During my PhD (1984-1990) under the supervision of Prof. J. G. Georgatos I worked on the isolation and characterization of plant lactose-hydrolyzing enzymes and their biotechnological application.

During my post-doc (1990-1994) as an EMBO fellow in the group of Dr. S.D. Georgatos, Cell Biology Program, EMBL, Heidelberg, I worked on the isolation and characterization of inner nuclear envelope proteins and their role in chromatin organization. My most significant contribution from this period was the identification and characterization of a protein complex formed by LBR (Lamin B receptor), the nuclear lamins, the LBR kinase and proteins p34 and p18 (*Simos and Georgatos, 1992; Simos et al., 1996*).

During the period 1995-2000, I worked as an assistant (Wiss. Assistent C1) in the group of Prof. Dr. Ed Hurt, in the Biochemie-Zentrum Heidelberg, Faculty of Medicine, University of Heidelberg where I also completed my *Habilitation* (academic teaching license; 2003). My work during this period involved mainly the genetic and biochemical analysis of the biogenesis and nuclear export of RNA in the yeast *S. cerevisiae*. My most important contributions included the identification and characterization of the yeast Arc1p-aminoacyl-tRNA synthetase complex (*Simos et al., 1996; Simos et al., 1998; Deinert et al., 2001; Galani et al., 2001*), the characterization of the yeast nuclear tRNA export receptor Los1p (*Hellmuth et al., 1998*), the discovery of an aminoacylation-dependent nuclear tRNA export pathway (*Grosshans et al., 2000*), the characterization of the tRNA modification enzyme Pus1p (*Simos et al., 1996; Grosshans et al., 2001*) and the delineation of the biogenesis of the signal recognition particle (*Grosshans et al., 2001*).

In 2001 I joined the Department of Biochemistry, School of Medicine, University of Thessaly, Larissa, Greece originally as Assistant and since Jan. 2007 as Associate Professor. I continued my work on yeast Arc1p (*Galani et al., 2005; Simader et al., 2006; Karanasios et*

al., 2007 & 2008) but I also initiated a new project focusing on the investigation of the human Hypoxia Inducible Factor HIF-1 α , a factor highly involved in many human diseases including cancer and cardiovascular disorders.

Both *in vitro* and *in vivo* systems were set up (Chachami et al., 2004; Chachami et al., 2005) and used in order to analyse the induction and function of HIF-1 α in smooth muscle cells (Chachami et al., 2007), the regulation of HIF-1 α by MAPK-dependent phosphorylation (Mylonis et al., 2006), its nuclear export (Mylonis et al., 2008), and nuclear import (Chachami et al., 2009) pathways and the identification of chemical compounds that inhibit its activity (Braliou et al., 2006; Triantafyllou et al., 2007 & 2008) and have, therefore, the potential to be used as anticancer agents. Related projects also include the involvement of hypoxia in the regulation of hepcidin secretion and iron homeostasis (Braliou et al., 2008) and analysis of HIF-1 α expression levels in patient samples.

As director of the Department of Biochemistry since March 2009, I am also coordinating the educational and research activities of the other staff members and especially their work dealing with aspects of the cellular response to hypoxia, which has become the central and common project of the Department.

I have co-authored 54 original research papers in peer-reviewed journals (10 as first and 20 as last author), 6 review articles and 2 book chapters. My publications have a total impact factor of 398 and have received 2.201 citations (*h-index*: 26)

Scientific publications

Original research articles in international scientific journals

A. Biotechnologically useful hydrolytic enzymes

1. Simos G., and J.G. Georgatsos (1988). Lactose-hydrolysing β -glycosidases of barley meal. *Biochim. Biophys. Acta* **967**, 17-24.
2. Simos G., Giannakouros T., and J.G. Georgatsos (1989). Plant β -galactosidases: Purification by affinity chromatography and properties. *Phytochemistry* **28**, 2587-2592.
3. Simos G., and J.G. Georgatsos (1990). Immobilization of barley β -glucosidase on solid supports - yields and properties. *Applied Microbiol. Biotechnol.* **33**, 51-53.
4. Giannakouros T., Karagiorgos A., and G. Simos (1991). Expression of β -galactosidase multiple forms during barley (*Hordeum Vulgare*) seed germination. Separation and characterization of enzyme isoforms. *Physiol. Plantarum* **82**, 413-418.
5. Simos G., Panagiotidis C.A., Skoumpas A., Choli D., Ouzounis C., and J.G. Georgatsos (1994). Barley β -glucosidase: Expression during seed germination and maturation and partial amino acid sequences. *Biochim. Biophys. Acta* **1199**, 52-58.

B. Interactions between the nuclear membrane, the nucleoskeleton and chromatin

6. Yuan J., Simos G., Blobel G., and S.D. Georgatos (1991). Binding of lamin A to polynucleosomes. *J. Biol. Chem.* **266**, 9211-9215.
7. Simos G., and S. D. Georgatos (1992). The inner nuclear membrane protein p58 associates in vivo with a p58 kinase and the nuclear lamins. *EMBO J.* **11**, 4027-4036.
8. Simos G., and S.D. Georgatos (1994). The lamin B receptor-associated protein p34 shares sequence homology and antigenic determinants with the splicing factor SF2-associated protein p32. *FEBS Lett.* **346**, 225-228.
9. Nikolakaki E., Simos G., Georgatos S.D., and T. Giannakouros (1996). A nuclear envelope-associated kinase phosphorylates arginine-serine motifs and modulates interactions between the lamin B receptor and other nuclear proteins. *J. Biol. Chem.* **271**, 8365-8372.
10. Simos G., Maison C., and S.D. Georgatos (1996). Characterization of p18, a component of the lamin B receptor complex and a new integral membrane protein of the avian erythrocyte nuclear envelope. *J. Biol. Chem.* **271**, 12617-12631.
11. Pyrpasopoulou A., Meier J., Maison C., Simos G., and S.D. Georgatos (1996). The lamin B receptor (LBR) provides essential chromatin docking sites at the nuclear envelope. *EMBO J.* **15**, 7108-7119.

12. Nikolakaki E., Meier J., Simos G., Georgatos S.D., and T. Giannakouros (1997). Mitotic phosphorylation of the lamin B receptor (LBR) by a serine/arginine kinase and p34^{cdc2}. *J. Biol. Chem.* **272**, 6208-6213.
- C. *Nucleocytoplasmic transport and tRNA biogenesis.*
13. Simos G., Tekotte H., Grosjean H., Segref A., Sharma K., Tollervey D., and E.C. Hurt (1996). Nuclear pore proteins are involved in the biogenesis of functional tRNA. *EMBO J.* **15**, 2270-2284.
14. Simos G., Segref A., Fasiolo F., Hellmuth K., Shevchenko A., Mann M., and E.C. Hurt (1996). The yeast protein Arc1p binds to tRNA and functions as a cofactor for the methionyl- and glutamyl-tRNA synthetases. *EMBO J.* **15**, 5437-5448.
15. Lecointe F., Simos G., Sauer A., Hurt E.C., Motorin Y., and H. Grosjean (1998). Characterisation of the yeast protein Deg1p as a pseudouridine synthase (Pus3) catalyzing the formation of Ψ38 and Ψ39 in tRNA anticodon loop. *J. Biol. Chem.* **273**, 1316-1323.
16. Simos G., Sauer A., Fasiolo F., and E.C. Hurt (1998). A conserved domain within Arc1p delivers tRNA to aminoacyl-tRNA synthetases. *Mol. Cell* **1**, 235-242.
17. Senger B., Simos G., Bischoff R., Podtelejnikov A., Mann M., and E.C. Hurt (1998). Mtr10p functions as a nuclear import receptor for the mRNA binding protein Npl3p. *EMBO J.* **17**, 2196-2207.
18. Motorin Y., Keith G., Simon C., Foiret D., Simos G., Hurt E., and H. Grosjean (1998). The yeast tRNA pseudouridine synthase Pus1p displays a multisite substrate specificity. *RNA* **4**, 856-869.
19. Santos-Rosa H., Moreno H., Simos G., Segref A., Fahrenkrog B., Pante N., and E.C. Hurt (1998). Nuclear mRNA export requires complex formation between Mex67p and Mtr2p at the nuclear pores. *Mol. Cell. Biol.* **18**, 6826-6838.
20. Hellmuth K., Lau D., Bischoff R., Künzler M., Hurt E.C., and G. Simos (1998). Yeast Los1p has properties of an exportin-like nucleocytoplasmic transport factor for tRNA. *Mol. Cell. Biol.* **18**, 6374-6386.
21. Hurt E., Hannus S., Schmelzl B., Lau D., Tollervey D. and G. Simos (1999). A novel in vivo assay reveals inhibition of ribosomal nuclear export in Ran-cycle and nucleoporin mutants. *J. Cell Biol.* **144**, 389-401.
22. Grosshans H., Hurt E. and G. Simos (2000). An aminoacylation-dependent tRNA export pathway in yeast. *Genes & Development* **14**, 830-840.
23. Hellmuth K., Grosjean H., Motorin Y., Deinert K., Hurt E. and G. Simos (2000) Cloning and characterization of the *Schizosaccharomyces pombe* tRNA:pseudouridine synthase Pus1p. *Nucleic Acids Res.* **28**, 4604-4610.
24. Deinert K., Fasiolo F., Hurt E. and G. Simos (2001). Arc1p organizes the yeast aminoacyl-tRNA synthetase complex and stabilizes its interaction with the cognate tRNAs. *J. Biol. Chem.* **276**, 6000-6008.
25. Grosshans H., Deinert K., Hurt E. and G. Simos (2001). Biogenesis of the signal recognition particle (SRP) involves import of SRP proteins into the nucleolus, assembly with the SRP-RNA and Xpo1p-mediated export. *J. Cell Biol.* **153**, 745-761.
26. Galani K., Grosshans H., Deinert K., Hurt E.C. and G. Simos (2001). The intracellular location of two aminoacyl-tRNA synthetases depends on complex formation with Arc1p. *EMBO J.* **20**, 6889-6898.
27. Grosshans H., Lecointe F., Grosjean H., Hurt E. and G. Simos (2001). Pus1p-dependent tRNA pseudouridinylation becomes essential when tRNA biogenesis is compromised in yeast. *J. Biol. Chem.* **276**, 46333-46339.
28. Lecointe F., Namy O., Hatin I., Simos G., Rousset J.P. and H. Grosjean (2002) Lack of pseudouridine 38/39 in the anticodon arm of yeast cytoplasmic tRNA decreases in vivo recoding efficiency. *J. Biol. Chem.* **277**, 30445-30453
29. Graindorge J.-S., Senger B., Tritch D., Simos G., and F. Fasiolo. (2005) Role of Arc1p in the modulation of yeast glutamyl-tRNA synthetase activity. *Biochemistry* **44**, 1344-1352.
30. Galani K., Hurt E. and G. Simos (2005). The tRNA aminoacylation co-factor Arc1p is excluded from the nucleus by an Xpo1p-dependent mechanism. *FEBS Lett.* **579**, 969-975.

31. Simader H., Hothorn M., Koehler C., Basquin J., Simos G., and Suck D. (2006). Structural basis of yeast aminoacyl-tRNA synthetase complex formation revealed by crystal structures of two binary sub-complexes. *Nucleic Acids Res.* **34**, 3968-3979.
 32. Karanasios E., Simader H., Panayotou G., Suck D. and G. Simos (2007) Molecular determinants of the yeast Arc1p/aminoacyl-tRNA synthetase complex assembly. *J. Mol. Biol.* **374**, 1077-1090.
 33. Karanasios E., Boleti H., and G. Simos (2008) Incorporation of the Arc1p tRNA-binding domain to the catalytic core of MetRS can functionally replace the yeast Arc1p/MetRS complex. *J. Mol. Biol.* **381**, 763-771.
- D. Molecular mechanisms of the cellular response to hypoxia*
34. Chachami G., Simos G., Hatziefthimiou A., Bonanou S., Molyvdas P.A., and E. Paraskeva (2004) Cobalt induces hypoxia-inducible factor-1alpha expression in airway smooth muscle cells by a reactive oxygen species- and PI3K-dependent mechanism. *Am. J. Respir. Cell Mol. Biol.* **31**, 544-551.
 35. Chachami G., Paraskeva E., Georgatsou E., Bonanou S., and G. Simos (2005). Bacterially produced human HIF-1alpha is competent for heterodimerization and specific DNA-binding. *Biochem. Biophys. Res. Com.* **331**, 464-470.
 36. Formento J.L., Berra E., Ferrua B., Magne N., Simos G., Brahimi-Horn C., Pouyssegur J. and G. Milano (2005) Enzyme-linked immunosorbent assay for pharmacological studies targeting hypoxia-inducible factor 1alpha. *Clin. Diagn. Lab. Immunol.* **12**, 660-664.
 37. Triantafyllou A., Liakos P., Tsakalof A., Georgatsou E., Simos G. and S. Bonanou (2006) Cobalt induces hypoxia-inducible factor-1 α (HIF-1 α) in HeLa cells by an iron-independent, but ROS-, PI-3K- and MAPK-dependent mechanism. *Free Radical Res.* **40**, 847-856.
 38. Braliou G.G., Venieris E., Kalousi A. and G. Simos (2006) Reconstitution of human hypoxia inducible factor HIF-1 in yeast cells: a simple in vivo system to identify and characterize HIF-1 α effectors. *Biochem. Biophys. Res. Com.* **346**, 1289-1296
 39. Mylonis I., Chachami G., Samiotaki M., Panayotou G., Paraskeva E., Kalousi A., Georgatsou E., Bonanou S. and G. Simos (2006) Identification of MAPK phosphorylation sites and their role in the localization and activity of Hypoxia-Inducible Factor 1 α . *J. Biol. Chem.* **281**, 33095-33106.
 40. Triantafyllou A., Liakos P., Tsakalof A., Chachami G., Paraskeva E., Molyvdas P.A., Georgatsou E., Simos G. and S. Bonanou (2007) Quercetin induces HIF-1 α expression and inhibits cell proliferation by depleting iron. *Free Radical Res.* **41**, 342-56.
 41. Chachami G., Hatziefthimiou A., Liakos P., Ioannou M.G., Koukoulis G.K., Bonanou S., Molyvdas P.-A. Simos G. and E. Paraskeva. (2007) Exposure of differentiated Airway Smooth Muscle cells to serum stimulates both induction of Hypoxia Inducible Factor-1 α and airway responsiveness to Ach. *Am. J. Physiol. Lung Cell Mol. Physiol.* **293**, 913-922.
 42. Lyberopoulou A., Venieris E., Mylonis I., Chachami G., Pappas I., Simos G., Bonanou S. and E. Georgatsou (2007) MgcRacGAP interacts with HIF-1 α and regulates its transcriptional activity. *Cell Physiol. Biochem.* **20**, 995-1006.
 43. Triantafyllou A., Mylonis I., Simos G., Bonanou S. and A. Tsakalof (2008) Flavonoids induce HIF-1 α but impair its nuclear accumulation and activity. *Free Radic. Biol. Med.* **44**, 657-670.
 44. Braliou G.G., Verga Falzacappa M.V., Chachami G., Casanovas G., Muckenthaler M.U. and G. Simos (2008) 2-Oxoglutarate-dependent oxygenases control hepcidin gene expression. *J. Hepatol.* **48**, 801-810
 45. Mylonis I., Chachami G., Paraskeva E. and G. Simos (2008) Atypical CRM1-dependent nuclear export signal mediates regulation of hypoxia-inducible factor-1alpha by MAPK. *J. Biol. Chem.* **283**, 27620-27627.
 46. Daponte A., Ioannou M., Mylonis I., Simos G., Minas M., Messinis I.E. and G. Koukoulis (2008) Prognostic significance of Hypoxia-Inducible Factor 1 alpha (HIF-1alpha) expression in serous ovarian cancer: an immunohistochemical study. *BMC Cancer* **8**, 335.
 47. Ioannou M., Sourli F., Mylonis I., Barbanis S., Papamichali R., Kouvaras E., Zafiriou E., Siomou P., Klimi E., Simos G., Roussaki-Schulze A.-V. and G. Koukoulis (2009) Increased HIF-1alpha immunostaining in psoriasis compared to psoriasisiform dermatitides. *J. Cutan. Pathol.* **36**, 1255-1261.

48. Ioannou M., Papamichali R., Kouvaras E., Mylonis I., Vageli D., Kerenidou T., Barbanis S., Daponte A., Simos G., Gourgoulisanis K. and G.K. Koukoulis (2009) Hypoxia inducible factor-1 alpha and vascular endothelial growth factor in biopsies of small cell lung carcinoma. *Lung* **187**, 321-9.
49. Chachami G., Paraskeva E., Mingot J.-M., Braliou G.G., Görlich D. and G. Simos (2009) Transport of hypoxia-inducible factor HIF-1 α into the nucleus involves importins 4 and 7. *Biochem. Biophys. Res. Commun.* **390**, 235-240.
50. Ioannou M., Mylonis I., Kouvaras E., Papamichali R., Daponte A., Paraskeva E., Simos G., and G. K. Koukoulis (2010) Validated analysis of HIF-1 α expression in cancer cells using a controlled and comparative immunoassay. *Oncology Reports*, **24**, 161-169.
51. Lakka A., Mylonis I., Bonanou S., Simos G. and A. Tsakalof (2010) Isolation of hypoxia-inducible factor 1 (HIF-1) inhibitors from frankincense using a molecularly imprinted polymer. *Investigational New Drugs*, **in press**.
52. Kalousi A., Mylonis I., Anastasia Politou A., Georgia Chachami G., Paraskeva E., and G. Simos (2010) Casein kinase 1 regulates human hypoxia-inducible factor HIF-1. *J Cell Science*, **in press**.
53. Mylonis I., Lakka A., Tsakalof A. and G. Simos (2010). The dietary flavonoid kaempferol effectively inhibits HIF-1 activity and hepatoma cancer cell viability under hypoxic conditions. *Biochem. Biophys. Res. Commun.* **in press**.
54. Papadakis A., Paraskeva E., Peidis P., Muaddi H., Li S., Raptis L., Pantopoulos K., Simos G. and A. Koromilas (2010) The eIF2 α kinase PKR modulates the hypoxic response by Stat3-dependent transcriptional suppression of HIF-1 α expression. *Cancer Research* **in press**.

Review articles in international scientific journals or books

1. Georgatos S.D., Meier J., and G. Simos (1994). Lamins and lamin- associated proteins. *Cur. Opin. Cell Biol.* **6**, 347-353.
2. Simos G., and E.C. Hurt (1995). Nucleocytoplasmic transport: factors and mechanisms. *FEBS Let.* **369**, 107-112.
3. Grosjean H., Szweykowska-Kulinska Z., Motorin Y., Fasiolo F., and G. Simos (1997). Intron-dependent enzymatic formation of modified nucleosides in eukaryotic tRNAs: A review. *Biochimie* **79**, 293-302.
4. Simos G. and E. Hurt (1999). Transfer RNA biogenesis: a visa to leave the nucleus? *Cur. Biol.* **9**, R238-R241.
5. Simos G. (1999). Nuclear export of tRNA. *Protoplasma* **209**, 173-180.
6. Grosshans H., Simos G. and E. Hurt (2000). Transport of tRNA out of the nucleus: Direct channeling to the ribosome? *J. Struct. Biol.* **129**, 288-294.
7. Simos G., Grosshans H. and E. Hurt (2002). Nuclear export of tRNA. *Results in Problems of Cell Differentiation* **35**, 115-31.
8. Simos G. (2002) Structure, function and biogenesis of the nuclear envelope in the yeast *Saccharomyces cerevisiae*. In the “*Dynamics of Nuclear Envelope Assembly in Embryos and Somatic Cells*”, Editor: P. Collas, Publisher: LANDES Biosciences.