CURRICULUM VITAE: Nicholas Grammatikakis, Ph.D.

Work Address:

Cell Signaling and Molecular Chaperones Laboratory, Director

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Position Title: Research Director **Place of Birth:** Lassithi, Crete

Citizenship: Greece/European Union (E.U.)

Current research activities

My general research expertise is in Cellular and Molecular Biology Research and, overall my graduate studies, training and work have all focused in the Signal Transduction in Cancer and in response to Stress. During the first part of my career (1982-1991), my laboratory investigations have focused experience in the areas of genomics and transcriptional gene regulation. Since 1992, working essentially as an independent investigator, I have focused on studying the basic mechanisms regulating cell signaling, cell cycle progression and cell transformation.

A) Cell Signaling

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Mechanisms of mammalian kinase regulation during normal differentiation and disease

Chemotherapeutical inhibition of oncogenic kinase activity

B) Cellular Responses to Stress

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Regulation of Chaperone Protein Activity

Identification of Signaling Mediators (including kinases and transcriptional factors) which are modulated by the Chaperone Machinery in transformed cells and in response to Stress

C) Cell Cycle Regulation

The Chaperone Machinery as an effector of cellular Stress in cell cycle progression

D) Novel Molecular Chaperones

Identification of novel Molecular Chaperones and study of their potential role as mediators of the assembly and activity of mammalian kinases in cell proliferation and cell cycle progression. Our study extends to learning how the activity of these novel signal modulators is regulated by

Growth conditions and Stress and in malignancy.

I have a long tracking record in research areas outlined above. For the last 16 years I have worked independently and I have been primarily responsible for designing and conducting experiments using various experimental models including cultured cells and animal models. During that time I have supervised and coordinated the efforts of laboratory staff (technical and students) in the field of Signaling Chaperones. In parallel, I have been involved in composing grants and editing all the manuscripts where I am the first or corresponding author (8 manuscripts in total).

Doctoral Dissertation:

In Molecular Biology: "Cloning and Functional Analysis of the Transferrin Gene", Department of Cell Biology and Human Genetics, the University of Texas Medical Branch at Galveston, Texas, 1989.

Previous Professional Experience:

---2001-2004: Research Assistant Professor, Center for the Molecular Stress Response, Boston University School of Medicine; Harvard University/ Beth Israel Deaconess Medical Center Boston, MA (Instructor). **Research topics**: Regulation of heat shock factor intracellular trafficking and activity and identification of signaling pathways involved; Regulation of the ErbB2 and NF-kappaB pathways by the chaperone machinery; HSF (Heat Shock Factor) isoforms and activity; Cdc37-mediated IKK assembly and activity.

--2000-2001: Research Associate, Department of Microbiology and Immunology, Queen's University, Kingston, ON. The role of molecular chaperones in LPS and TNFa-mediated signaling in macrophages; Study of a specialized group of chaperones and chaperone cofactors serving as partners and potential regulators of viral oncoproteins (SV40 Large-T, Hepatitis B reverse transcriptase, Tax and Tat).

--10/2001-4/2001: Research Associate, Lankenau Instritute

--1995-2000: Research Associate, Dept. of Physiology, Tufts Univ., Boston, MA (laboratory of Dr B. Cochran). Regulation of Raf-1 by the Cdc37/Hsp90 chaperone system; Identification and study of components of native mammalian kinase complexes; Characterization of a kinase-specific chaperone pathway in the production of a Cdk9/Cyclin T1 heterodimer during P-TEFb-mediated Tat stimulation and HIV-1 transcription.

--1991-1995: Postdoctoral Fellow, Dept. of Anatomy and Cell Biology, Tufts Univ., Boston, MA (laboratory of Dr Bryan Toole). Hyaluronan-receptors in malignancy; Isolation and study (structure-function) of the Cdc37 family proteins in human, mouse and chicken; Regulatory roles of Cdc37, Hsp90 and other members of the chaperone machinery in signal transduction; Regulation of Cdk4/Cyclin D assembly and activity by the chaperone machinery. --1982-1989: Ph.D. Candidate, University of Texas Medical Branch and NCI/FCRF (laboratories of Drs L. Chan and J. Papaconstantinou). Isolation and study of the regulation of the transferrin and the transferrin receptor genes; Transcriptional regulation of viral and cellular genes by viral oncoproteins of the HTLV family. Education:

1982-1989: University of Texas Medical Branch, Galveston, TX (Ph.D. in Molecular Biology) **1977-1982:** School of Biology, University of Thessaloniki, Greece (B.Sc. in Biology) **1976-1977:** Agricultural University of Thessaloniki, Greece.

Awards and Fellowships:

10/2005: Research Program was evaluated by the General Secretariat for Research and Technology (Ministry of Development, Greece) as one of the three most promising at the Institute of Biology (National Centre for Scientific Research "Demokritos"/ see APPENDIX)

4/2002: American Cancer Society Award for Beginning Investigators. Title of the study: "The IKK regulator p50 cdc³⁷ as a potential LMP1 effector and target in cancer chemotherapy".
 4/2001: Queen's Postdoctoral Fellowship.

1997-2000: Research supported by the US/DOD Breast Cancer Research Program.

1996-1997: Supported by L.P. Markey Award (Tufts University).

1987-1989: Research supported by National Cancer Institute Fellowship (NCI/FCRF).

1982-1987: Graduate studies supported by full State Fellowship.

1982: I was awarded one of the two Scholarships given by of the Hellenic Scholarship Foundation for Graduate studies in England (declined).

1976-1982: Government Scholarship, awarded to top 10 out of 150 candidates on admission, and subsequently awarded each year until graduation for being among the top ten in each year

Teaching and Supervising Experience:

--1980-1982: As a 3rd and 4th year undergraduate student (University of Thessaloniki) I worked closely with Dr Nitska Beis in establishing a complete series of undergraduate labs for the Biology students. During that time, I also assisted Professor C. Arsenis in editing a three-volume textbook on Developmental Biology.

As a graduate student I taught labs in Cell Biology to the 2nd year medical students (University of Texas).

--1992-1995: I taught "Molecular Biology Techniques" to graduate students of the Sackler School of Graduate Studies (Tufts University).

In addition, I have supervised and directed the work of a great number of colleagues, including: Elizabeth Gerhardt, Jeanette Banks, Mark Eckley (1982-1989), Masahiko Yoneda, Aliki Siganou, Alfredo Sabbah, Santra Panse, Conrado Jones, Michael Alexandrakis, Lei Huang, Qin Yu, Majieh Kotecki, and Jay Lee (1991-2000), Shen Gan, Melik Okzoz, Adina Vultur and Hideobu Takahashi (2001-2004). At the NCSR Demokritos, I have supervised a research technician (Aliki Siganou) and the work of two Ph.D. candidates (Sofia Aliberti and Avraam El Hamidie).

Patents granted: "Vertebrate Cdc37" Country: WO World Intellectual Property Organization (WIPO) World-Wide Patent Number: WO9801463A1 Application Number: WO1997US0011737 Date Issued: Jan.15, 1998

Inventors: Grammatikakis N, et. al.,

"Nucleic acids encoding vertebrate Cdc37"

Country: USA USA Patent Number: US6066723 Application Number: US1996000675885 Date Issued: May 23, 2000 Inventors: Grammatikakis N, *et. al.*,

Scientific Articles:

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2. **Grammatikakis N**. Cloning and functional analysis of the murine transferrin gene. (Doctoral Dissertation, The University of Texas Medical Branch at Galveston, Texas, 1989).

3. Pavlakis G, Felber B, Kaplin G, Paskalis H, **Grammatikakis N**, and Rosenberg M 1989. Regulation of expression of the HTLV family of retroviruses. In The Control of Human Retrovirus Gene Expression (Franza BR, Jr, Cullen BR, and Wong-Staal F, eds.), CSH Press, Cold Spring Harbor, NY, pp. 281-289.

4. **Grammatikakis N**, Grammatikakis A, Yoneda M, Yu Q, Banerjee SD, Toole BP. A novel glycosaminoglycan binding protein is the vertebrate homologue of the cell cycle control protein, Cdc37. **J Biol Chem** 1995, Jul 7; 270(27): 16198-205.

5. **Grammatikakis N**, Toole BP. Functional domain mapping using M13 deletions. Biochemistry and **Mol Biol Int** 1995; 36(4): 771-9.

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7. Yu Q, **Grammatikakis N,** Toole BP. Expression of multiple CD44 isoforms in the apical ectodermal ridge of the embryonic mouse limb. **Developmental** 1996; 207(2):

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Paper No.10 (**Grammatikakis N** (Corresponding Author), Lin JH, Tsihlis P., Cochran BH. p50(cdc37) acting in concert with Hsp90 is required for Raf-1 function. **Mol. Cell. Biol.**

1999; 19(3): 1661-72) has been characterized as a "ground breaking" in the field; and has attracted close to 200 citations (self-references not included).

Appentix:

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Η τελευταία αξιολόγηση του Ινστιτούτο Βιολογίας από την διεθνή επιτροπή κατά την αξιολόγηση των Ερευνητικώ ν Κέντρων της χώ ρας, Γενική Γραμματεία Έρευνας και Τεχνολογίας (ελήφθη από την ιστοσελίδα της GGET) PHASE 2 EVALUATION REPORT

INSTITUTE OF BIOLOGY

NATIONAL CENTRE OF SCIENTIFIC RESEARCH "DEMOKRITOS"

October 11, 2005

General Comments

The Institute of Biology (IB) has a diverse research agenda. It is striving to be competitive in three general areas identified as Programs. The Programs are:

Program A: Regulation of Cellular Function/Age-Related Diseases

Program B: Model Biological Systems for the Study of Cellular Functions

Program C: Structural and Computational Biology

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The Programs have two thrusts, biomedicine and biotechnology, which, in turn, are divided into the following topics.

In vitro models of cancer, diabetes, senescence, and neurodegenerative diseases

Molecular mechanisms of normal cellular signaling

Changes occurring in diseased conditions

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Development of pharmaceuticals, diagnostics and therapeutics to interfere with these diseases or their progress and complications

Genetic and biotechnological approaches for the development of insect cell and viral vectors for recombinant proteins of agricultural importance

Proteins of medical relevance with the prospect of gene therapy

The IB is one of eight institutes in the National Center for Scientific Research "Demokritos" (NCSR). Significantly, it represents life sciences in a center that is dedicated primarily to nuclear physics and technology, materials science, informatics/telecommunications and radio-technological applications. As such, it appears to be an island unto itself despite the newly established collaboration with the Institutes of Physical Chemistry and Materials Science to develop and use new biomedical and nanoscience-related approaches for interfering with certain human diseases. Within the IB, there are four special laboratories listed.

Human Tissue Bank

Animal Facility

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Structural Unit

Confocal Microscopy

There are 18 Researchers in the IB with the rank of Researcher A, B or C (2004 data). This number represents approximately 14% of the Researchers in the NCSR. Based on total income (total expenditure) from regular public budget funding, public investment funds and EU framework programs, the IB income represents 6.7% of the NCSR income (2004 data).

Assessment of the IB

Research in the IB is varied and broad ranging—a factor that has prevented the Institute from becoming recognized nationally and internationally. The only program that enjoys true

international recognition is Insect Molecular Genetics and Biotechnology led by Dr. K. latrou. It has great potential for biotechnological applications in agriculture, medicine and the environment. All areas can be leveraged scientifically and commercially. However, the highest payoff would be in agricultural and environmental applications. Dr. latrou is an accomplished scientist. He has vision and foresight. He is industrious, hard-working and creative. He appears to have good people skills and is highly organized.

All other research areas in the IB are diffuse with no obvious focus although there is an attempt to relate several research projects to age-related diseases such as diabetes, senescence and cancer, among others. From this particular effort, one unifying theme does emerge—cell signaling. The IB has a window of opportunity, albeit rapidly closing, to become premier in molecular signaling as it relates to oncogenesis and cell death. Research in this area would be useful for identifying potential drug targets. The development of radio-diagnostics also has potential but the efforts in this area are not well defined or coordinated. Dr. D. Kletsas is a bright and shining star who, with appropriate and adequate support, could bring prominence to a research program that emphasizes cellular signaling and cell-cell communication. Dr. N. Grammatikakis is a valuable addition to the IB who also could help establish the Institute as an international leader in this important and exciting area of science. These two investigators should be able to formulate a research program in cellular signaling, with the help of other scientists in the Institute, which is second to none. Their presence in Greece provides a tremendous opportunity to promote basic science in the Country as well as to attract attention and financial support from the pharmaceutical industry.

An additional program area that deserves considerable attention in terms of funding support is Structural and Computational Biology led by Drs. M. Vlassi and M. Pelecanou. This program area could be an integral part of the two aforementioned program areas as well as provide some service outside the Institute. Furthermore, this program area should be able to stand on its own by attracting a considerable amount of extramural funding from the government of Greece, the EU and private industry. Regretfully, the funding level for the entire program is insufficient. Dr. Vlassi has had moderate success in securing research monies whereas Dr. Pelecanou has not been very successful in this regard. Dr. Pelecanou has an excellent scientific publication record both in quantity and quality whereas Dr. Vlassi has been much less productive. The lack of research focus is a serious problem for this program area. Another problem in this program area is the lack of support personnel and insufficient funds for repair and maintenance of the equipment. The x-ray crystallographic system is less than state-of-the-art despite the statement to the contrary in the IB Business Plan. The NMR spectrophotometers are adequate for a variety of research applications although there should be serious consideration of acquiring higher resolution NMR capability. Overall, the current instrumentation available to this program area is not of the caliber suitable to support world-class research in structural biology. If this program area is to flourish, considerable effort and money need to be expended to bring it up to internationally competitive standards.

In spite of the weaknesses and problems mentioned above, this particular research area holds much promise. The program needs immediate direction. It needs to be led by one person either by Dr. Vlassi, Dr. Pelecanou or an individual recruited from outside the Institute. Dr. Pelecanou obviously is an aggressive and productive scientist. Given adequate support and consideration, she should be able to turn the program around and point it in the right direction. Otherwise, a new person should be recruited immediately. The program needs an infusion of new money (at least $1.5M \in$) from within Greece to purchase new instrumentation and hire support personnel.

The productivity of each individual scientist in the IB is given in Table 1. The data indicate the amount of competitive funds received by each individual serving as a principal investigator (Coordinator). It does not take into account monies received from collaborative grants. The number of publications is a quantitative index of the productivity of each researcher. It does not reflect the "quality" of science accomplished nor does it indicate the contribution made by each person to each paper published or to science in general. However, it does reflect the wide variation in research funding and productivity among the scientists.

Table 1. Productivity of individual scientists

Name

Total Amount of Funding (€)*

Number of Publications in Refereed Journals

- 1.
- Υ. Almrantis
- 0
- 7
- 1.
- Georgoussi Z.

164,814

2

1.

N. Grammatikakis

71,740

16

1.

K. latrou

1,307,500

13

1.

P. Kitsiou

90,000

4

1.

D. Kletsas

97,720

13

1.

V. Labropoulou

0

0

1.

M. Pelecanou

23,500

17

1.

A. Prombona

0

3

1.

K. Sekeri-Pataryas

12

24,460

1.

E. Sideris

0

9

1.

V. Sophianopoulou

161,800

8

1.

T. Sourlingas

32,608
13
1. K. Stamatakis
0
1
1. L. Swevers
0
7
1.

E. Tsilibary

187,466

6 1. Tzinia Α. 50,000 4 1. Vlassi Μ. 207,646 4

*Competitive funds received by individuals listed as Coordinator in the Business Plan (2004 data)

Recommendations

Βιογραφικό Σημείωμα Υπευθ. Εργαστηρίου - Institute of Biosciences & amp; Applications

Reorganize the IB into two new institutes, one that encompasses insect molecular genetics and biotechnology and another that involves cellular signaling and human disease.

Appoint Dr. latrou as Institute Director for Insect Molecular Genetics and Biotechnology.

Appoint Dr. Kletsas as Institute Director for Cellular Signaling and Human Disease.

Assign the most productive scientists in the IB to either of the two institutes as appropriate.

Relocate both institutes to other research centers.

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If the above recommendations are not possible, the following actions should be taken:

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Reorganize the IB into two program areas: (i) insect molecular genetics and biotechnology and (ii) cellular signaling and human disease with Dr. latrou and Dr. Kletsas serving as program leaders of the respective units.

2.

Upgrade the structural biology unit so that it can stand alone as a single program area and appoint a highly qualified individual to lead the program.

3.

Integrate the three program areas so that true synergy can be realized.

4.

Recruit a new director of the IB from outside the Institute. A national/international search is necessary.