Constantinos E. Vorgias PhD

Professor of Biochemistry

PRESENT AFFILIATION

Professor of Biochemistry,
Department of Biochemistry-
Molecular Biology,
Faculty of Biology,
National and Kapodistrian
University of Athens

ACADEMIC QUALIFICATIONS

- University of Athens School of Natural and Mathematic Sciences, Faculty of Biology (1980)
- Post Graduate Research Fellow in Biology Department of the Nuclear Research Centre "Demokritos, Athens, Greece (1981)
- Ph-D fellowship from Max-Planck Department for Cell Biology, Heidelberg, Germany, Prof. Dr. Peter Traub. PhD thesis from the Natural Sciences Faculty of Karls Ruprecht Heidelberg University, Germany (1981-1985)

MANAGEMENT EXPERIENCE

- 1985-1987: Military Service as Lieutenant in Reserve.
- 1989-1996: Scientific and organizational supervisor at the European Molecular Biology Laboratory (EMBL) Hamburg Outstation.
- 2005-2007: Selected as Vice-President of the Faculty of Biology, Athens University.
- 2005-2008: Member of the central organization committee for FEBS 2008 in Athens.
- 2005-2007: Member of the National Research and Technology Committee.
- 2006-2011: Member and President of the Greek National Scholars Examination Committee (2006-2011)
- 2009-2010: Director of the Department of Biochemistry-Molecular Biology, Faculty of Biology, Athens University.
- 2010-now: Vice Technical Supervisor of the School of Life Sciences, Athens University.

OFFICE ADDRESS

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MEMBER OF NATIONAL AND INTERNATIONAL SCIENTIFIC SOCIETIES

- Active Member of the European Chitin Society since 1993
- Active Member of the Greek Biological Society since 1981
- Active Member of the Greek Biochemical Biophysical Society since 1985
- Active Member of the Hellenic Crystallographic Society, since 2001
- President of the ALUMNI Heidelberg in Athens Greece, since 2002.
- Active member of the Greek Society for Biosciences, since 2004.
- President of the Greek Biotechnological Society, since 2006

PROFESSIONAL ACTIVITIES

- 1981: Post-graduate fellowship award from the Greek Ministry for Atomic Energy.
- 1981-1984: Ph-D fellowship from Max-Planck Department for Cell Biology, Heidelberg, Germany, Prof. Dr. Peter Traub (1981-1984).
- 1983: A week training course from Waters for HPLC applications
- 1984-1985: Visiting scientist at the European Molecular Biology Laboratory, Heidelberg, Germany Structural department. Prof. Dr. D. Tsernoglou.
- 1985-1987: Military service in the Greek army, lieutenant in reserve.
- 1988-1989: Senior scientist fellowship of the Biotechnology Program of European Community. Max-Planck Institute for Biophysical Chemistry, Department for Molecular Genetics, Goettingen, Germany, Prof. Dr. D. Galwitz.
- 1988: A week training course for the production and application of monoclonal antibodies. University of London, Royal Postgraduate Medical School, Wolfson Center, London, UK.
- 1989-1996: Staff Scientist at the European Molecular Biology Laboratory, Hamburg-Outstation. Head of Biochemistry-Molecular Biology Laboratory.
- 1991: Short-term fellowship award from European Molecular Biology Organization (EMBO) to visit Marie Curie Institute in Paris (May 1991).
- 1991: Tutor in a 3 weeks training course in New Dehli, India. Nucleic Acid Synthesis and Gene Assembly. Molecular Genetics Laboratory of the International Center for Genetic Engineering and Biotechnology.
- 1996-1999: Assist. Professor of Biochemistry at the Department of Biochemistry-Molecular Biology, Faculty of Biology of National and Kapodistrian University of Athens.
- 1998: Senior Researcher Fellowship award of the DGXII of EU Biotechnology program, Visiting Professor at the Technical University of Harburg – Hamburg (Summer 1998).
- 1999-2002: Assist. Professor of Biochemistry (Tenure) at the Department of Biochemistry-Molecular Biology, Faculty of Biology of National and Kapodistrian University of Athens.
- 2000 Summer: Visiting Professor supported from the Max-Planck Society to work at the MPI Institute for Cell Biology, Heidelberg, Germany (2000).
- 2002-2007: Assoc. Professor of Biochemistry at the Department of Biochemistry-Molecular Biology, Faculty of Biology of National and Kapodistrian University of Athens.
- 2003: DAAD Senior Research award as visiting Professor at the Technical University of Harburg-Hamburg (2003).
- 2005: Visiting Professor award of Hans Kupczyk Foundation at the Ulm University (2005).

SCIENTIFIC PUBLICATIONS / CITATIONS

- In international journals and books, about 100 publications with a citation index above 3000 and impact factor over 300. Current H factor 26.
- Over 140 contributions in national and international conferences and workshops.
- Invited speaker in over 30 national and international conferences and lectures.
- Over 40 Diplom thesis
- About 20 Diplom Master thesis
- 10 PhD student

- 2006: DAAD Senior Research award as visiting Professor at the Technical University of Harburg-Hamburg (2006).
- 2007-now: Elected as Full Professor of Biochemistry at the Department of Biochemistry-Molecular Biology, Faculty of Biology of National and Kapodistrian University of Athens.
- 2009: DAAD Senior Research award as visiting Professor at the EMBL Hamburg-Germany- Ulm and Regensburg Universities (Summer 2009).
- 2010-2011: Responsible for the building maintenance of the School of Natural Sciences of Athens University
- 2010-2013: Member of the international PhD program of the Polish Research Foundation (Polish Academy of Science, POZNAN)
- 2010: Organization of the 1st International School at the University of Athens in cooperation with Ulm University (International Post Graduate School). Protein structure and function and Kinases as drug targets. Sept 2010, 22-26.
- 2011: Four months Sabbatical with short visits at: EMBL Hamburg (GR), Netherlands Cancer Institute (NL), Polish Academy of Science (PL), Ulm University (DE), Imperial College (UK) (2-5, 2011).
- 2011: Co-organizer at the International Conference on Enzyme Science and Technology ICEST 2011, 31.10-4.11.2011 Kusadasi, Turkiye.
- 2011: Organization of the 1st summer school at the Faculty of Biology of Athens University with the title: Proteins: from the gene to the structure and more…" 1-3 July 2011.
- 2011: Organization of the 2nd International School at the University of Athens in cooperation with Ulm University (International Post Graduate School). Biochemical, Molecular Biology and structural basis of the biology of stem cells. Sept 2011, 20-24.
- 2012: DAAD Senior Research award as visiting Professor at the Ulm University (Summer 2012).
- 2012: Organization of the 2nd summer school at the Faculty of Biology of Athens University with the title: Proteins: from the gene to the structure and more…" 18-20 May 2012.

INVITED SPEAKER IN NATIONAL AND INTERNATIONAL FORA

- 1992: Lecture at the Max-Planck for Cell Biology, Department of Prof. P. Traub. May.
- 1993: Speaker at the 5th Symposium on Chitin Enzymology, Senigallia, AN, Italy, 10-12 May, 1993.
- 1993: Lecture at the Biochemistry Department of the Medical School of Kiel University, Oct. 1993.
- 1994: Lecture at the Hebrew University, Jerusalem, Haddash Medical School. Aug. 1994.
- 1994: Lecture at the IMBB, Enzyme Technology. Prof. B. Bouriotis, Sept. 1994.

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FUNDING

- I have received the following competitive grants:
- EU Framework II, Human Capital and Mobility.
- EU Framework III, Human Capital and Mobility.
- EU, Framework III, Scientific Cooperation of the EU with the 3rd Mediterranean Countries.
- EU, Framework IV, Biotechnology (area 6)
- EU, Framework IV, Biotechnology (area 1)
- EU, Framework V, Quality of Life Area.
- 4 grants DAAD (German Academic Exchange Service)
- 1 grant from IKYDA (IKY+DAAD)
- 1 grant from Human Frontiers (HF)
- 1 grant from NATO Science for Peace (SFP)
- 12 grants from the Greek Ministry of Development National and International Cooperations.
- 4 Internal Grants from Athens University
- 1 grant from the private foundation "Eugenidion"

- 1995: Lecture at the Advanced FEBS Course on Methods in Protein Sequence Analysis. Apr. 30-May, 5 Chalkidiki Greece (1995)
- 1996: Lecture at the Bonn University, Department of Chemistry and Biochemistry, Aug 1996.
- 1996: Invited Speaker and Chairman at the 2nd International Symposium on Chitin Enzymology, Senigallia, AN, Italy, 8-11 May, 1996
- 1997: Invited Speaker and Chairman at the 7th International Conference on Chitin and Chitosan Sept 3-5,
- 1997, Lyon France. Invited speaker
- 1997: Lecture at the Hellenic Research Foundation, Athens Greece, 3.2.1997
- 1997: Invited Speaker and Chairman at the 7th International Conference on Chitin and Chitosan Sept 3-5, 1997, Lyon France.
- 1998: Invited speaker and Chairman at the 2nd International Conference on Extremophiles Aug. 1998, Brest France.
- 2000: Chairman at the 3rd International Conference on Extremophiles, Sept. 3-7, 2000 Hamburg.
- 2001: Chairman at the 4th European Conference on Chitin Enzymology, May. 6-10, 2001, Ancona, Italy
- 2002: Invited Speaker and Chairman at the Biocat 2002, Hamburg Technical University, NIT, Germany
- 2004: Lecture at the Hellenic Kidney Association, March, 2004, Athens
- 2004: Lecture at the National University of Australia, J. Curtis Medical School, 9. 11. 2004, Canberra, Australia.
- 2005: Lecture at the Ulm University (Biology Department, Institute of Endocrinology) 01.2004
- 2005: Lecture at the Ulm University (Medical School, Department of Internal Medicine) 01.2004
- 2005: Nomination Lecture at the Ulm University (invited from the Ulm University President).
- 2007: Lecture at the Advances in Kidney Research, 18.2.2007 Divani-Caravel, Athens (Chairman)
- 2007: Lecture at the Cyprus University, Biological Science Dept. 2. 2. 2007, Nicosia, Cyprus.
- 2009: Lecture at the Department of Biophysical Sciences, Regensburg University, 7. 2009.
- 2011: Invited Speaker and Chairman at the International Conference on Enzyme Science and Technology ICEST 2011, 31.10-4.11.2011 Kusadasi, Turkiye.
- 2012: Invited Lecture at the University of Patras 10. 5. 2012. Workshop on Structural Biology.

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PUBLICATIONS IN INTERNATIONAL JOURNALS AND BOOKS

1. Nelson W. J., Vorgias C. E. and Traub P. (1982) A rapid method for the large scale purification of the intermediate filament protein vimentin by single-stranded DNA cellulose affinity chromatography. Biochem. Biophys. Res. Commun. 106, 1141-1147.
2. Traub P., Nelson W. J., Kühn S. and Vorgias C. E. (1983) The interaction *in vitro* of the intermediate filament protein vimentin with naturally occurring RNAs and DNAs. J. Biol. Chem. 258, 1456-1466.
3. Vorgias C. E. and Traub P. (1983) Isolation of glial fibrillary acidic protein from bovine brain white matter and its purification by affinity chromatography on single-stranded DNA cellulose. Biochem. Biophys. Res. Comm. 115, 68-75.
4. Traub P. and Vorgias C. E. (1983) Involvement of the N-terminal polypeptide of vimentin in the formation of intermediate filaments. J. Cell Sci. 63, 43-67.
5. Vorgias C. E. and Traub P. (1983) Isolation, purification and characterisation of the intermediate filament protein desmin from porcine smooth muscle. Prep. Biochem. 13, 227-243.
6. Traub P. and Vorgias C. E. (1984) Differential effect of arginine modification with 1,2-cyclohexanedione on the capacity of vimentin and desmin to assemble into intermediate filaments and to bind to nucleic acids. J. Cell Sci. 65, 1-20.
7. Traub P., Vorgias C. E. and Nelson W. J. (1985) Interaction *in vitro* of the Neurofilament Triplet Proteins from Spinal Cord with Natural RNAs and DNAs. Mol. Biol. Rep. 10, 129-136.
8. Vorgias C. E. and Traub P. (1986) Nucleic acid-binding activities of the intermediate filament subunits desmin and glial fibrillary acidic protein. Z. Naturforsch. 416, 897-909.
9. Vorgias C. E. and Traub P. (1986) Efficient degradation *in vitro* of all intermediate filament subunits proteins by the Ca^{2+}-activated neutral thiol proteinase from Ehrlich Ascite Tumor cells and procine kidney. Bioscience Reports 6, 57-64.
10. Zimmermann H.-P., Plagens U., Vorgias C. E. and Traub P. (1986) Changes in the organization of non-epithelial intermediate filaments induced by triethyl lead chloride. Exp. Cell Res. 167, 360-368.
11. Kuehn S., Vorgias C. E. and Traub P. (1987) Interaction *in vitro* of non-epithelial intermediate proteins with supercoiled plasmid DNA. J. Cell Sci. 87, 543-554.

PUBLICATIONS IN INTERNATIONAL JOURNALS AND BOOKS

12. Vorgias C. E., Peridis G. A., Traub P. and Sekeris C. E. (1988) Colchicine, colcemide and cytochalasin-b do not affect translocation of the glucocorticoid hormone-receptor in rat thymocytes or Ehrlich Ascites cells. Bioscience Reports 8, 193-197.

13. Gallwitz D., Haubruck H., Molenaar C., Prange R., Putzicha M., Schmitt H.-D., Vorgias C. E. and Wagner P. (1988) Structural and functional analysis of *ypt* proteins, a family of *ras*-related nucleotide-binding proteins in eucaryotic cells. In: The Guanine - Nucleotide Binding Proteins, Common Structural and Functional Properties, Edited by L. Bosch, B. Kraal and A. Parmeggiani, NATO ASI Series, Life Sciences Vol. 165, 257-264.

14. Haubruck H., Prange R., Vorgias C. E. and Gallwitz, D. (1989) The *ras*-related mouse *ypt1* protein can functionally replace the YPT1 gene product in yeast EMBO J. 8, 1427-1432.

15. Wilson K. S., Vorgias C. E., Tanaka I., White W. S. and Kimura M. (1990) The thermostability of DNA binding protein HU from thermophilic and mesophilic *bacilli.* Protein Engineering 4, 11-22.

16. Vorgias C. E., Kingswell A. J., Dauter Z., Wilson K. S. (1991) Cloning, overexpression, purification and crystallisation of ribosomal protein L9 from *Bacillus stearothermophilus.* FEBS Lett. 286, 204-208.

17. Vorgias C. E., Lemaire H-G., Wilson K. S. (1991) Overexpression and purification of the galactose operon enzymes from *E. coli.* Protein Expr. Purif. 2, 330-338.

18. Vorgias C. E. and Wilson K. S. (1991) A rapid method for the purification of recombinant integration host factor. Protein Expr. Purif. 2, 317-320.

19. Padas M. P., Wilson K. S. and Vorgias C. E. (1992) DNA binding protein from mesophilic and thermophilic *bacilli*: cloning, overexpression and purification. Gene 117, 39-44.

20. Vorgias C. E., Kingswell A. J., Dauter Z. and Oppenheim A. B. (1992) Crystallisation of recombinant chitinase from the cloned *chi*A gene of *Serratia marcescens.* J. Mol. Biol. 226, 897-898.

21. Tews I., Dauter Z., Oppenheim A. B. and Vorgias C. E. (1992) Crystallisation of recombinant chitobiase from *Serratia marcescens.* J. Mol. Biol. 228, 696-697.

22. Sayers Z., Brouillon P., Vorgias C. E., Nolting H. F., Hermes C. and Koch M. H. J. (1993) Cloning and expression of *Saccharomyces cerevisiae* copper-metallothionein gene in *Escherichia coli* and characterisation of the recombinant protein. Eur. J. Biochem. 212, 521-528.

PUBLICATIONS IN INTERNATIONAL JOURNALS AND BOOKS

23. Vorgias C. E., Tews I., Perrakis A., Wilson K. S. and Oppenheim, A. B. (1993) Purification and characterisation of the recombinant chitin degrading enzymes chitinase and chitobiase from *Serratia marcescens*. In Chitin Enzymology (Muzzarelli, R. A. A. ed.) pp 417-422.

24. Perrakis A., Wilson K. S., Chet. I., Oppenheim, A. B. and Vorgias C. E. (1993) Phylogenetic relatioships of chitinases. In Chitin Enzymology (Muzzarelli, R. A. A. ed.) pp 217-232.

25. Rypniewski W. R., Perrakis A., Vorgias C. E. and Wilson K. S. (1994) Evolutionary divergence and conservation of trypsins. Protein Eng. 7, 57-64.

26. Vis H., Boelens R., Mariani M., Stroop R., Vorgias C. E., Wilson K. S. and Kaptein R. (1994) ^{1}H, ^{13}C and ^{15}N resonance assignments and secondary structure analysis of the HU protein from *Bacillus stearothermophilus* using two- and three-dimensional double- and triple-resonance heteronuclear magnetic resonance spectroscopy. Biochemistry 33, 14858-14870.

27. Perrakis A., Tews I., Dauter Z., Wilson K. S. and Vorgias C. E. (1994) X-ray structure analysis of Chitinase A from *Serratia marcescens*. In Chitin World (eds Karnicki, Z.S., Wojtasz-Pajak, A., Brzeski, M.M. and Bykowski, P.J.) pp 408-415.

28. Tews I, Vincentelli R., Perrakis A., Dauter Z., Wilson K. S. and Vorgias C. E. (1994) Primary and 3D-analysis of chitobiase from *Serratia marcescens*. In Chitin World (eds Karnicki, Z.S., Wojtasz-Pajak, A., Brzeski, M.M. and Bykowski, P.J.) pp 415-423.

29. Perrakis A., Tews I., Dauter Z., Oppenheim, A. B., Chet I., Wilson K. S. and Vorgias C. E. (1994) Crystal structure of a bacterial chitinase at 2.3 Å resolution. Structure 2, 1169-1180.

30. Vis H., Mariani M., Vorgias C. E., Wilson K. S., Kaptein R. and Boelens R. (1995) Solution structure of the HU Protein from *Bacillus stearothermophilus*. J. Mol. Biol. 254, 692-703.

31. Sitrit Y., Vorgias C. E., Chet I. and Oppenheim A. B. (1995) Cloning and primary structure of a *chi*A gene from *Aeromonas caviae*. J. Bacteriology 177, 4187-4189.

32. Sikorski M. M., Topunov A. F., Strozycki P. M., Vorgias C. E., Wilson K. S. and Legoski A. B. (1995) Cloning and expression of plant leghrmoglobin cDNA of *Lupinus luteus* in *Escherichia coli* and purification of the recombinant protein. Plant Science 108, 109-117.

33. Boelens R., Vis H., Vorgias C. E., Wilson K. S. and Kaptein R. (1996) Structure and dynamics of the DNA binding protein HU from *Bacillus stearothermophilus* by NMR Spectroscopy. Biopolymers 40, 553-559.

PUBLICATIONS IN INTERNATIONAL JOURNALS AND BOOKS

34. Tews I., Perrakis A., Dauter Z., Oppenheim A. B., Wilson K. S. and Vorgias C. E. (1996) Bacterial chitobiase structure provides insight into catalytic mechanism and the basis of Tay-Sachs disease. Nature Structural Biology 3, 638-648.

35. Vis H., Vageli O., Nagel J., Vorgias C. E., Wilson K. S., Kaptein R. and Boelens R. (1996) NMR study of the interaction of the HU protein from *Bacillus stearothermophilus* with DNA. Magnetic Resonance in Chemistry 34, 81-86.

36. Tews I., Vincentelli R. and Vorgias C. E. (1996) N-acetylglucosaminidase (chitobiase) from *Serratia marcescens*: gene sequence, and protein production and purification in *Escherichia coli*. Gene 170, 63-67.

37. Tews I., Wilson K. S. and Vorgias C. E. (1996) Enzymatic mechanism of N-acetylglucosaminidase revealed by structural studies on enzyme substrate-inhibitor complexes. Advances in Chitin Science Vol. 1. pp. 26-33.

38. Perrakis A., Ouzounis C. Wilson K. S. and Vorgias C. E. (1996) Implications of the 3-D structure determination of family 18 chitinases. Similarities with FnIII domains, oviductal proteins and narbonins. Advances in Chitin Science Vol. 1. pp 34-41.

39. Kanellopoulos P. N., Pavlou K., Perrakis A., Aganian B., Vorgias C. E., Mavrommatis C., Soufi M., Tucker P. A. and Hamodrakas S. J. (1996) The crystal structure of the complexes of Concanavalin A with 4'-nitrophenyl-a-D-mannopyranoside and 4'-nitrophenyl-a-D-glucopyranoside. J. Struct. Biol. 116, 345-355.

40. Vorgias C. E., Perrakis A. and Tews I. (1996) Structure function studies on the chitinolytic enzymes of *Serratia marcescens* chitinase and chitobiase. Annals of the New York Academy of Science. 799, 190-192.

41. Perrakis A., Tews I. and Vorgias C. E. (1996) Chitinases, Hevamine and Chitobiases: "Faraway and yet so closed" In Chitin Enzymology (Muzzarelli, R. A. A. ed.) Vol 2, pp 109-122.

42. Tews I., Wilson K. S. and Vorgias C. E. (1996) Structural studies on N-acetylglucosaminidase enzyme-inhibitor complexes In Chitin Enzymology (Muzzarelli, R. A. A. ed.) Vol 2, pp 213-225.

43. Fernandes M. J. G., Leclerc D., Henrissat. B., Vorgias C. E., Gravel R., Hechtman P. and Kalpan F. (1997) Identification of candidate active site residues in lysosomal beta-hexosaminidase A. J. Biol. Chem. 272, 814-820.

44. Chernin L. S., De la Fuente., Sobolev V., Haran S., Vorgias C. E., Oppenheim A. B. and Chet I. (1997) Molecular cloning, structural analysis and Expression in *Escherichia coli* of a chitinase gene from *Enterobacter agglomerans*. Appl. Env. Microbiology 63, 834-839.

PUBLICATIONS IN INTERNATIONAL JOURNALS AND BOOKS

45. Spindler-Bath M., Blattner R., Vorgias C. E. and Spindler K-D. (1998) Inhibition of two family 18 chitinases by various allosamidin derivatives. Pestic. Sci. 52, 47-52.

46. Joergensen S., Vorgias C. E. and Antranikian G. (1997) An exttracellular alpha-amylase from the hypethermophilic Archeon *Pyrococcus furiosus*. Cloning, Sequencing, Characterization and Expression in *E. coli* and *Bacillus subtilis*. J. Biol. Chem. 272, 16335-16342.

47. Drouillard S., Armand S., Davies G., Vorgias C. E. and Henrissat B. (1997) *Serratia marcescens* chitobiase is a retaining glycosidase utilising substrate acetamido group participation. Biochem. J. 328, 945-949.

48. Vorgias C. E. (1997) Overproduction of the recombinant chitinase A from *Serratia marcescens* in *E. coli*, fast purification, biochemical and biophysical characterisation. Chapter in Chitin Handbook (Muzzarelli and Peter eds.) ISBN 88-86889-01-1.

49. Vorgias C. E. and Petratos K. (1997) From the purified protein to the 3D-structure and enzymatic mechanism of chitinase A from the chitinolytic soil bacterium *Serratia marcescens*. Chapter in Chitin Handbook Chapter in Chitin Handbook (Muzzarelli and Peter eds.) ISBN 88-86889-01-1.

50. Vorgias C. E. (1997) Structural basis of chitin hydrolysis in bacteria. Advances in Chitin Society Vol II, pp. 176-187.

51. Christodoulou E. and Vorgias C. E. (1998) Cloning, overproduction, purification and crystallisation of the DNA binding protein HU from the hyperthermophilic eubacterium *Thermotoga maritima*. Acta Cryst. D54, 1043-1045.

52. Vis H, Vorgias C. E., Wilson K. S., Kaptein R. and Boelens R. (1998) Mobility of NH bonds in DNA-binding protein HU of *Bacillus stearothermophilus* from reduced spectral density mapping analysis at multiple NMR fields. J. Biomolecular NMR 11, 265-277.

53. Vorgias C. E. and Antranikian G. (2000) Glycosyl Hydrolases from Extremophiles in Glycomicrobiology, pp313-339 (ed. by Doyle) Kluwer Academic/Plenum Publishers, N. York

54. Boehlke K., Pisani F. M, Vorgias C. E., Frey B., Sobek H., Rossi M. and Antranikian G. (2000) PCR performance of the B-type DNA polymerase from the thermophilic euryarchaeon *Thermococcus aggregans* improved by mutations in the Y-GG/A motif. Nucleic Acids Res. 28, 3910-3917.

55. Prag G., Papanikolau Y., Tavlas G., Vorgias C. E., Petratos K. and Oppenheim A. B. (2000) Structures of chitobiase mutants complexed with the substrate di-N-acetyl-D-glucosamine: the catalytic role of the conserved acidic pair, aspartate-539 and glutamate-540. J. Mol. Biol. 300, 611-617.

PUBLICATIONS IN INTERNATIONAL JOURNALS AND BOOKS

56. Fontaine T., Simenel C., Dubreucq G., Adam O., Delepierre M., Lemoine J., Vorgias C. E., Diaquin M. and Latgé J-P. (2000) Molecular organization of the alkali-insoluble fraction of *Aspergillus fumigatus* cell wall. J. Biol. Chem. 275, 27594-27607.

57. Lonhienne T. G. A., Mavromattis C., Vorgias C. E, Buchon L., Gerday C. and Bouriotis V. (2001) Cloning, sequences, and characterization of two chitinase genes from the antarctic *Arthrobacter* sp. strain TAD20: Isolation and partial characterization of the enzymes. J. Bacteriology 183, 1773-1779.

58. Lonhienne T. G. A., Zoidakis J., Vorgias C. E, Feller G., Gerday C., and Bouriotis V. (2001) Modular structure, local flexibility and cold-activity of a novel chitobiase from a psychrophilic antartic bacterium J. Mol. Biol. 310, 291-297.

59. Christodoulou E., Duffner F. and Vorgias C. E. (2001) Overexpression, purification and characterization of a thermostable Chitinase (Chi40) from *Streptomyces thermoviolaceus* OPC-520. Protein Expr. Purif. 23, 97-105.

60. Papanikolau Y., Prag G., Tavlas G., Vorgias C. E., Oppenheim A. B. and Petratos K. (2001) High-resolution structural analyses of mutant Chitinase A complexes with substrates provide new insight into the mechanism of catalysis. Biochemistry 40, 11338-11343.

61. Prog G., Vorgias C. E. and Oppenheim, A. B. (2001) Conservation and structural elements and catalytic mechanism in *Serratia marcescens* chitinolytic enzymes. Chitin Enzymology, 2001. Ancona pp. 351-360.

62. Raves M. L., Doreleijers J., Vis H., Vorgias C. E., Wilson K. S. and Kaptein R. (2001) Joint refinement as a tool for thorough comparison between NMR and X-ray data and structures of HU protein. J. Biomolecular NMR 21, 235-248.

63. Christodoulou E. and Vorgias CE. (2002) The thermostability of the DNA binding protein HU from mesophilic, thermophilic and extreme thermophilic bacteria. Extremophiles 6, 21-31.

64. Christodoulou E. and Vorgias C. E. (2002) Understanding heterologous protein overproduction under the T7 promoter: A practical exercise. Biochemical and Mol. Biol. Education 30, 189-191.

65. Bernard M., Mouyna I., Dubreucq G., Debeaupuis J.-P., Fontaine T., Vorgias C. E., Fuglsang C. and Latgé J-P. (2002) Characterization of a cell wall acid phosphatase in *Aspergillus fumigatus.* Microbiology 148, 2819-2829.

PUBLICATIONS IN INTERNATIONAL JOURNALS AND BOOKS

66. Christodoulou E., Rypniewski W. and Vorgias C. E. (2003) High resolution X-ray structure of the DNA binding protein HU from the hyperthermophilic eubacterium *Thermotoga maritima* and the determinants of its thermostability. Extremophiles 7, 111-122.

67. Papanikolau Y., Vorgias C. E. and Petratos K. (2003) De novo purification scheme and crystallization conditions yield high-resolution structures of chitinase A and its complex with the inhibitor allosamidin. Acta Crystallogr. D 59: 400-403.

68. Serban D, Arcineigas S. F., Vorgias C. E., Thomas G. J Jr. (2003) Structure and dynamics of the DNA-binding protein HU of *B. stearothermophilus* investigated by Raman and ultraviolet-resonance Raman spectroscopy. Protein Sci 12(4): 861-870.

69. Andronopoulou E, Vorgias C. E. (2003) Purification and characterization of a new hyperthermostable, allosamidin-insensitive and denaturation-resistant chitinase from the hyperthermophilic archaeon *Thermococcus chitonophagus*. Extremophiles 7:43-53.

70. M. A. Durney, R. W. Wechselberger, C. G. Kalodimos, R. Kaptein, C E. Vorgias, and R.Boelen (2004) An alternate conformation of the hyperthermostable HU protein from *Thermotoga maritima* has unexpectedly high flexibility. FEBS Lett. 563, 49-54.

71. Vorgias, C. E., Antranikian, G. (2004) Extremophiles: pH, temperature, and salinity. Alan T. Bull (ed.) Microbial Diversity and Bioprospecting, ASM Press, Washington, D.C. p. 146-153 (586 pages) ISBN 1-55581-267-8.

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Constantinos E. Vorgias PhD
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CURRENT RESEARCH ACTIVITIES

During my 30 years research activities in Germany and in Greece I have established a broad spectrum of cooperations in various countries within Europe and Israel. In most of the case these projects are my initiative and I have taken the management of the projects as well.

The projects are briefly presented. The involved partners and the publication listed according the publication list of my curriculum vitae are also presented.

Protein structure-function and protein engineering studies on a variety of members of the HU histone like DNA binding proteins from procaryotes and archaea towards understanding their thermostability mechanism and interaction with DNA.

HU is a highly conserved protein that is believed to play an important role in the architecture and dynamic compaction of bacterial DNA. Its ability to control DNA bending is crucial for functions such as transcription and replication. The crystal structure of HU from *Bacillus stearothermophilus* (HU*Bst*) has been solved and refined at 2**A**. The solution structure of the recombinant HU from *Bacillus stearothermophilus* expressed in *E. coli* has also been determined by NMR. HU*Bst* protein has been used as a model system to study protein-DNA interaction(s) of the histone-like protein family which includes the integration host factor (IHF) protein. The structural properties responsible for the thermostability of HU proteins from mesophilic and thermophilic microorganisms attracted our attention during the last two decades. The HU proteins from *Bacillus stearothermophilus* and *Bacillus subtilis* have been analyzed with respect to their sequence characteristics in correlation to their thermostability. We have expanded our studies on the HU protein to extreme thermophilic organisms, such as the eubacterium *Thermotoga maritima* (growth temperature 80-85°C) which shows 61% and 51% identity to HU from the thermophilic *Bacillus stearothermophilus* and the mesophilic *Bacillus subtiliis*, respectively. The small size of the HU molecule and the existence of homologous proteins in various bacteria, from psychroplic to mesophilic up to extreme thermophilic, makes it an attractive model to address questions of thermostability using the structural-mutational approach. Engineering proteins for thermostability is a particularly exciting and challenging field, as it is crucial for broadening the industrial use of recombinant proteins. Many experimental approaches have been applied to identify determinants of thermostability. The structure-mutational approach was applied predominantly, but it is time consuming and expensive, and requires proteins that are highly conserved in their primary structure and are present in organisms which grow at low and high temperature. Therefore, only a limited number of proteins has been studied based on this approach. The interaction of HU with DNA have been studied in solution using a variety of high resolution biophysical methods.

Partners: 1, 4, 5, 13

Publication no: 15, 18, 19, 26, 30, 33, 35, 51, 52, 62, 63, 64, 66, 68, 70, 72, 74, 82, 90, 94, 103

Presentations no: 7, 8, 9, 13, 17, 18, 19, 20, 21, 43, 47, 64, 91, 99, 101

Constantinos E. Vorgias
Professor of Biochemistry

CURRENT RESEARCH ACTIVITIES

Protein structure-function and protein engineering studies on two bacterial chitin degradation enzymes, chitinases and chitobiase from procaryotes and archaea towards understanding their mechanism for catalysis, adaptation to various temperatures and substrate recognition.

Chitin is abundant in nature, second after cellulose, as a crucial structural component of the cell walls of fungi and certain green algae, and as a major constituent of shells, cuticles and exoskeletons of worms, molluscs and arthropods, including crustaceans and insects. Chitin and its partially deacetylated derivative, chitosan, as well as other derivatives exhibit interesting properties and constitute a valuable raw material for biomedical, agricultural, cosmetics, and innovative biotechnological applications. In the aquatic biosphere, approximately 10^{11} tons of chitin is produced annually.

Chitinases (EC 3.2.1.14) hydrolyse the ß-1,4-linkages in chitin. The chitinases, currently sequenced or identified, are classified into two families, 18 and 19, within the glycosyl-hydrolases superfamily established by Henrissat and Bairoch, based on the amino acid sequence similarity of their catalytic regions. Family 18 contains chitinases from bacteria, fungi, viruses, animals, and some plant chitinases. Family 19 contains plant chitinases and a few bacterial chitinases, such as *Streptomyces griseus* chitinase C. Chitinases of the two families do not share amino acid sequence similarity, have various 3D-structures and enzymatic mechanisms, and are therefore likely to have evolved from diverse ancestors. Bacterial chitinases generally consist from multiple functional domains such as chitin-binding domain (ChBD) and fibronectin type III-like domain (Fn3 domain) linked to the catalytic domain. The involvement of the ChBD in the degradation of insoluble chitin has been analysed for a few bacterial chitinases.

The first structures of chitinase A and chitobiase have been determined from our group and several chitinases genes for various bacterial and archaea have been analyzed.

Currently we are working with chitinases from the marine environment. The major part of the marine biosphere is characterized by permanent low temperatures (-2–10°C) and therefore is a good source of cold-adapted marine bacteria, the so-called psychrophilic bacteria. Chitin is a very abundant insoluble biopolymer in the marine environment. Chitinases produced by psychrophilic bacteria, responsible for degradation of the krill chitin, should have high catalytic activities under these low-temperature conditions and most often, if not always, exhibit high thermosensitivity. These properties can be very useful for various applications. In the past few years, several psychrophilic enzymes have been and the primary structure of some of them has been determined. Until recently, few psychrophilic chitinases have been isolated from bacteria and fungi, however only a catalytic domain of one other psychrophilic chitinase, from *Arthrobacter* TAD20, has been solved (pdb code 1kfw). We have determined

and report the crystal structure of a chitinase 60 (chi60) from the psychrophilic bacterium *Moritella marina*. The enzyme has been examined in complexes with the reaction intermediate, with the reaction product and in an unliganded form. SAXS experiments are in accordance with the crystal structure data. A remarcable property of chi60 is its folding-unfolding reversibility as determined by Circular Dischroism and Deifferential Scanning Microcalorimetry studies. To my knowledge is the first psychrophilic TIM-barrel enzyme showing this properties and from the point of protein engineering and design it is worth to study by applying rational design and directed evolution approach.

Partners: 1, 3, 5, 13

Publication no: 20, 21, 23, 24, 27, 28, 29, 34, 36, 37, 38, 40, 41, 42, 43, 44, 45, 47, 48, 49, 50, 53, 55, 56, 57, 58, 59, 60, 61, 65, 67, 69, 73, 75, 76, 77, 83, 87, 89, 98, 102, 103, 104.

Presentations no: 22, 23, 24, 25, 26, 27, 30, 32, 34, 35, 37, 38, 44, 45, 46, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 63, 65, 67, 69, 71, 72, 74, 75, 76, 79, 80, 81, 82, 84, 85, 98, 100, 111, 114, 140.

Design of new inhibitors specific for chitobiase/hexosaminidase

Chitobiase(ChB) belongs to GH20 family that catalyses the final step of chitin degradation to beta-1,4 linked 2-acetamido-2-deoxy-glucopyranosyl (NAG). Due to its homology with hexosaminidases catalytic domain, known to be responsible for Tay-Sachs and Sandhoff diseases, structural studies of chitobiase could serve as a model for testing potential inhibitors against the aforementioned diseases. We have reproduced the crystallisation conditions of ChB from Serratia marcescens as describe by Tews et al. [1]. [1].Tews I, Perrakis A, Oppenheim A, Dauter Z, Wilson KS, Vorgias CE. (1996) Bacterial chitobiase structure provides insight into catalytic mechanism and the basis of Tay-Sachs disease. Nat Struct Biol. 3, 638-48. We are currently studying the effect NAG analogues, already identified as potent inhibitors of GlcNAcase from *S. marcescens* in the nM range, in complex with chitobiase. The ultimate aim of this collaborative project is to use these compounds as leads for the design of specific hexosaminidase inhibitors.

Partners: 1, 15

Publication no: 34, 43, 47, 105

Presentations no: 33, 36, 42, 130, 133.

Elucidation of the folding-unfolding reversibility mechanism of the thermostable TIM-barrel enzyme chitinase-40 (Chi40) by rational design and directed evolution

The TIM-barrel fold is abundant in various enzyme families, catalyzing completely different biochemical reactions. Its remarkable versatility is further highlighted in proteins from extremophiles due to the environment in which these enzymes work. Chi40, a thermophilic chitinase that was found to adopt the TIM-barrel fold, exhibits reversibility after thermal denaturation. In order to determine

structural factors that might underlie this phenomenon, extensive molecular modeling studies of the enzyme were employed. The results indicate that Chi40 shares homologous sequential and structural characteristics with both thermophilic and psychrophilic TIM-barrel chitinases that have been crystallographically determined. After the construction of the 3D-model of the enzyme, and in accordance with sequence and structure analysis results, analysis indicated that Chi40 may intrinsically drive its correct refolding: it is suggested that reversibility mainly depends on the distribution of key residues along the secondary structure elements. It is assumed that Pro residues and sequence fragments promote the formation of helices. Helix-helix and helix-loop interactions might be involved in the initial step of the refolding. During the formation of the core, ß-strands start to form a ß-sheet, and therefore contribute to the collapse of the helical core and its replacement by a steadier one, formed by a ß-barrel, following a Zip and Assembly folding mechanism. The proposed mechanism is clearly theoretical, but does not violate previous DSC and CD data. It might provide insight into the explanation of how a big, TIM-barrel enzyme can find its way out of local minima points, avoiding the exposure of large hydrophobic areas to the solvent, and finally adopt its functional fold. Experimentally the proposed mechanism will be elucidated by combination of rational design and directed evolution technology.

Partners: 1, 3.

Publication no: 59, 83, 102

Presentations no: 105

Molecular biology of various stress responses of lactic bacteria

The collaboration between my group and Prof. Tsakalidou's group started back in 2003 during the PhD thesis of Konstantinos Papadimitriou that received a "Herakleitos" grant by the Greek Ministry of Education. I supervised Kostas during the final part of his PhD when he attempted to identify acid stress responsive genes in the bacterium *Streptococcus macedonicus*. Our collaboration was extended during the PhD thesis of Ioanna Asteri and we cloned, sequenced and characterized a number of native plasmids from food isolated lactic acid bacteria. Both Kostas and Ioanna received their PhD degree with merit. Other topics that we focused on were the transcriptional changes of *Lactobacillus acidipiscis* under high salt stress and the generation and characterization of *Lactococcus lactis* mutants that are resistant to the bactericidal effect of Macedocin produced by *Streptococcus macedonicus*.
We are currently starting a new project concerning the structure-function relationship of the hydrophilin protein GsiB that is produced by *Bacillus subtilis*.
Up to now our collaboration has resulted in 4 research publications and 16 abstracts in national and international conferences. A number of articles are also in different stages of preparation.

CURRENT RESEARCH ACTIVITIES

Partners: 1, 11.

Publication no: 88, 92, 95, 96, 105.

Presentations no: 103, 112, 119, 120, 121, 123, 124, 128, 129, 131, 132, 134, 135, 138, 139.

Breast cancer stem cells resistance mechanisms in genotoxic insults: Applications in diagnosis, personalized treatment strategies and prognosis of disease progression.

Project in the initial phase and has received financial support from the national program "Thalis"

Chemoresistance of cancer stem cells is considered as one of the major causes of tumor recurrence often resulting in enhanced aggression and poor prognosis of the median survival. Particularly, treated triple negative breast tumors (ER/PR and/or HER2) present high rates of recurrence accompanied by frequent and varied metastases and short life expectancy for the patients.

The key objective of this proposal is a systematic analysis of the major underlying mechanisms responsible for the resistance of cancer stem cells to genotoxic damages caused by treatment schemes. These mechanisms are thought to include DNA repair mis-regulation as well as ROS inactivation.

At the outset of the project, the expression of DNA repair key molecules, representing major DNA repair pathways, will be examined in MCF7 derived cancer stem cells and $CD44^{+}/CD22^{-/low}ALDH1^{+}$ breast cancer stem cells from patient biopsies. The DNA repair capability of these cells will be further investigated at the gene expression and protein level. In parallel, cancer stem cells, isolated from patients, will be cultured in primary cultures and their intrinsic ability to effectively repair their genome will be examined (WP 4). The obtained results will be evaluated in relation to at least a 4-year follow-up of patients and in correlation to the treatment protocols followed. Mono-and multiparametric statistical analysis will be additionally incorporated in the study.

In conclusion, the proposal is expected to: a) further elucidate the mechanisms involved in DNA repair regulation, b) support the design of more effective personalized treatment protocols, c) promote prognosis of breast cancer progression, d) train young researchers and e) establish a core research network from various disciplines at National level with a potential to be expanded at European level. Such a network would enable us to disseminate the results of our project in a more integrative manner with expected strong socio-economic benefits.

Partners: 1, 6, 8, 10, 12, 14, 17.

Constantinos E. Vorgias
Professor of Biochemistry

CURRENT RESEARCH ACTIVITIES

Interaction of Rad51 with p53 and BRCA2: Single substitutions in amino-acid residues of Rad51, located in the area interacting with p53 and BRCA2, dramatically alters Rad51's behaviour.

Structural modification of Rad51, a key enzyme in the high fidelity mechanism of homologous recombination repair (HRR) of DNA, results in major miss-localization of the protein from cytoplasm to the nucleus. More precisely, point mutations in the region of Rad51 implicated in interaction with two key tumour suppressors, p53 and BRCA2, were designed, expected to modify the conformation of the region. A couple of these mutants, possibly by altering complex formation with partner molecules, resulted in migration of the Rad51 to the cell nucleus, in the absence of DNA damage. Both of these mutant forms are able to interact with Rad51wt, probably blocking its normal function. Especially Phe166Ala-Rad51 expression resulted in cell cycle progress modification accompanied by changes in protein expression patterns of factors involved in cell cycle and cell fate control. These results further support a key role of Rad51 in interconnecting HRR pathway to cell cycle progress and cell survival. Apparently, such tools apart from essentially contributing in further delineating HRR pathway, they can also be utilised as potential anti-tumour drugs, enabling cancer cell targeting and elimination due to either HRR dysfunction or hyper-recombination events.

Partners: 1, 3, 6, 8.

Publication no: 97, 99, 100, 108

Presentations no: 57, 70, 73, 104, 108, 109, 113, 117, 118, 122, 125, 126.

Dental cone beam ct irradiation effects on molecules involved in maintenance of genome integrity.

The Dental Cone Beam CT (DCBCT) has been specifically developed for dental use as it can offer a volume 3-dimensional imaging similar to medical CT but with significantly lower radiation exposure of the patient. Nevertheless, ionizing irradiation is a source of DNA damage. Hitherto, DNA damage caused by DCBCT has been examined only in macromolecular level, i.e. as shown by micronuclei formation. The current study focuses on determining DCBCT irradiation consequences in molecular level by examining alterations in factors involved in DNA damage signaling, accurate DNA repair, as well as cell cycle control and apoptosis. Characteristic foci of phosphorylated γH2AX, a marker of ds DNA damage, were clearly detected in HEK293 cell nuclei, in just half an hour after irradiation. In accordance, altered protein levels of crucial molecules involved in DNA repair such as BRCA1 and Rad51, were observed. More specifically, BRCA1 protein was significantly induced at least half an hour after irradiation, while Rad51 protein sustained quite higher than normal levels 48 h following irradiation. Our data clearly imply that DCBCT irradiation of HEK293 cells results in at least temporary modification of molecules involved in DNA

damage detection and repair. BRCA1 is implicated in detection of DNA damage and further regulation of the consequent repair processes, while Rad51 is a key factor of homologous recombination, a high fidelity DNA repair mechanism. Still, further studies are definitely required for a more concrete evaluation of DCBCT irradiation risk assessment at the molecular level.

Partners: 1, 10, 12.

Presentations no: 136.

Structure-function studies on LMKT3 and CK1δ.

In a recent publication in Nature Medicine, Giamas *et al.* (2011) performed a short interfering RNA (siRNA) screen in order to identify novel regulatory kinase targets modulating the estrogen receptor alpha (ERα) pathways. ERα is expressed in more than 2/3 of human breast cancers and current therapies lead to relapse, while resistance to existing therapies is also common. Clearly, there is a need for novel therapeutics that will effectively regulate ERα expression. Lemur Tyrosine Kinase 3 (LMTK3, gene on human chr. 19; 19p13.33), a serine/threonine-protein kinase, was identified among the most potent regulators of ERα. LMTK3 acts upon downstream targets to enhance expression of ERα, while it phosphorylates the estrogen receptor to protect it from proteosomal degradation. The protein is a single-span membrane bound protein consisting of 1460 amino acids, which encode a single peptide, a transmembrane helix followed by a cytoplasmic tail. In order to conduct biochemical analyses on LMTK3 and characterise the kinase further. We have received 5 plasmids encoding either the full length protein, or the catalytic site (or part of the active site), aiming to express these in mammalian or insect cells, using appropriate vectors. Currently we have managed to get adequate amount of recombinant protein for further drug screening and biochemical and structural analyses.

Partners: 1, 3, 6, 7, 9, 15

Publication no: 85, 86

Presentations no

Development and screening of novel, rationally designed IAPP (amylin) variant/analogue-peptides as drugs for diabetes type II

Normally soluble proteins or peptides convert under certain conditions into ordered fibrillar aggregates, known as amyloid fibrils. These fibrils appear to be related to several neurodegenerative diseases including Alzheimer's, Parkinson's. Huntington's, and, also, type II diabetes, prion diseases and many others, called amyloidoses. Amyloidogenesis is related to the presence of short sequence stretches (amyloidogenic determinants/aggregation 'prone' sequences). A consensus prediction algorithm (http://biophysics.biol.uoa.gr/AMYLPRED) predicts successfully nearly all experimentally verified

determinants and also predicts an amyloidogenic potential for several additional stretches with a hitherto unknown role on amyloidogenesis. Islet amyloid polypeptide (IAPP, also called amylin), a 37 amino acid residue peptide, is stored in insulin-secretory granules and secreted by pancreatic ß-cells acting, together with insulin, as regulator of glucose homeostasis. IAPP is associated with type II diabetes, a disease affecting more than 350 million people worldwide. There is mounting evidence for the importance of amyloid formation, deriving from amyloid fibrils containing mature IAPP, associated with type II diabetes. A recently developed IAPP variant (Symlin/Pramlintide) is marketed as an antidiabetic drug, since 2008. We propose to: (a) design, with the tool AMYLPRED, non-amyloidogenic variants of IAPP, either full length or partial, (b) synthesize and purify these variants with protein engineering/biochemical or classical synthetic chemistry methods, (c) investigate theoretically and experimentally folding and self-assembly mechanisms of amyloidogenesis of these synthesized peptides (selecting only those with non-amyloidogenic properties), (d) screen their functional/cytotoxicity properties on properly selected cultured human cells and, (e) select, for future animal/clinical trials, the most-promising variants as possible drugs against diabetes type II and obtain suitable patents for them.

Partners: 2, 1.

Presentations no

Preparation of 2 proposals for EU.

Peptide-linked small molecule scaffolds as new concept to develop specific protein kinase inhibitors.

In current drug discovery projects, an increasing number of protein kinases (PK) have been shown to be validated targets for drug development. A number of protein kinase inhibitors (PKI) have been developed into the clinic, offering novel or second line therapeutic options (LIT). However, approved drugs commonly show therapy-limiting features such as lack of specificity and efficacy, development of cancer cell resistance, and severe side effects (LIT). Therefore, there is an urgent need to develop novel PKI with increased specificity and clinical efficacy. Chemical discovery efforts to develop PKI have produced compounds like ATP-competitive ligands, allosteric regulators, and irreversible binders. So far, the majority of PKI bind to the highly conserved ATP pocket of PK (type I/II binders). Several of these ATP-mimicking inhibitors have gained some specificity and potency. On the other hand, small molecules that bind to allosteric pockets outside the ATP cleft offer significant higher potential for selective PK inhibition because these sites are highly divergent across the kinome. In contrast to the established procedures to develop ATP-competitive binders, even structure-based design of allosteric drugs is still a technical and

experimental challenge. As a key difficulty, the high demand of specific allosteric interactions is not met by the low complexity of conventional ligand libraries currently used for screening. Our alternative innovative hybrid-approach, outlined in this proposal, is based on the nM affinity of a non-selective small molecule PKI, which is combined with additional peptide-protein interactions outside the ATP site to gain more specificity. The basic idea is to generate innovative scaffolds consisting of a potent but non-selective small molecule binder covalently linked to a highly diverse oligopeptide library based on mRNA display technology. Structure-based molecular modeling will be used to design a suitable linker between the small molecule and the cell permeable peptide moiety of the mRNA display library. This hybrid-molecule library providing a variability of up to 10^{13} individual scaffolds will be screened against validated drug targets to identify highly affine and specific candidates. Compared to established technology, such as phage display, the complexity of our novel hybrid-molecule library is 10^5 higher thus significantly increasing the likelihood of a successful identification of suitable library members with excellent ligand specificity and affinity. Selected individual scaffolds showing high affinity and specificity will be cloned, sequenced, and produced synthetically. Next, we will characterize promising scaffolds *in vitro* and *in vivo*, including tissue culture and animal models. Furthermore, scaffold-protein interactions will be structurally determined and analyzed at the molecular level.

Partners 1, 2, 3, 6, 7, 15

An integrated concept for monitoring and evaluating the physicochemical and biological parameters of various groundwater model systems (polluted in various ways) towards early warning and contaminant source identification for assuring resource sustainability.

Water is the most important and delicate natural resource in our planet. Anthropogenic activities have considerably influenced the quality of our sweet aquatic ecosystem that encountered around 5% of the total water on the earth. This problem is generally considered to be one of the top priorities worldwide.

A detailed multidisciplinary study of selected aquatic model systems in Europe, particularly related to groundwater resources located close to heavily polluting sources like industry and intensive agriculture is the major objective of this project.

The suggested approach will focus on two basic goals:

- Developing an early warning system and prediction of contaminant fate
- Identification of the origin of groundwater contamination

The first will require the establishment of a groundwater monitoring network for early and fast monitoring of the aquifer's quality characteristics via the

CURRENT RESEARCH ACTIVITIES

evaluation of physicochemical parameters and biological markers in an integrated manner based on micro or nano-technological platforms. The implementation of a groundwater flow and contaminant transport simulation model will enable us to predict the fate of the potential pollutants and to alarm for taking measures to protect public health. For these purposes, raw data concerning physicochemical and biological measurements in the groundwater samples will be carried out periodically not only in situ but in the laboratory as well.

The second objective aims at creating a reliable suite of combined physicochemical, isotopic and biological markers for the discrimination of contamination sources. This identification of the origin of contamination in the groundwater system will help in understanding the processes affecting local contaminant concentrations and will be necessary for:

- The improved management of groundwater bodies for preserving water quality and assuring resource sustainability
- Actions for the remediation of contaminated sites that can be targeted to the actual source making them more efficient

A number of Central European countries including Israel and Ireland will assemble a task force consortium, coordinated by Athens University with common goal to collect, summarize and validate the state of the art in relation to our approach. This action will enhance the basic knowledge of the groundwater ecosystem particularly the C and N cycles, the remediation capacity and its response to various high load pollutants in certain model systems.

The objectives of this study will be achieved at geological, physicochemical, biochemical (element cycles), microbiological and molecular level by:

- Integrating the currently used parameters (physicochemical and isotopic)
- Enhancing the data with highly specific biomarkers
- Developing a model platform for the validation of the combined parameters
- Developing an early warning system
- Developing a web-based dissemination center (GIS supported)
- Developing a reliable suite of markers for the differentiation of sources of contamination

Partners 1, 11, 16 and 3 more others under negotiations

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