

PERSONAL INFORMATION**SURNAME: GIANNAKAKIS****NAME: ANTONIS****DATE OF BIRTH: 8 MARCH 1980****PLACE OF RESIDENCE: ALEXANDROUPOLIS****e-mail: antgian@mbg.duth.gr****WEBSITE: <http://theranostics.mbg.duth.gr/>****CURRENT POSITIONS**

- 11.2018 – 06.2022** **Assistant Professor in Computational Molecular Biology**, Dept. Molecular Biology and Genetics (MBG), Health Science School, Democritus University of Thrace (DUTH), Alexandroupolis, Greece.
Tenured
- 07.2022 –** Ongoing position
- 05.2019 –** **Researcher C on Non-coding RNAs and Computational Molecular Biology**, University Research Institute for the Study of Genetic & Malignant Disorders in Childhood, Choremeion Research Laboratory, Agia Sofia General Pediatric Hospital of Athens, National & Kapodistrian University of Athens, Greece.

PREVIOUS POSITIONS

- 11.2021 – 11.2023** **Vice-president of the Hellenic Society of Computational Biology and Bioinformatics**
- 01.2018 – 08.2018** **Senior Research Fellow**
Hellenic Institute of Pasteur (HPI), DIANA-lab, Athens, Greece.
- 10.2016 – 08.2018** **Senior Research Fellow**
University Research Institute for the Study of Genetic & Malignant Disorders in Childhood, Choremeio Research Center, A' Department of Pediatrics, National and Kapodistrian University of Athens, Agia Sofia General Pediatric Hospital of Athens, Greece.
- 11.2009 – 08.2016** **Post-doc Research Fellow**
Agency for Science, Technology and Research (A*STAR), Bioinformatics Institute, Division of Genome and Gene Expression Data Analysis, Singapore.
- 08.2005 – 12.2007** **Visiting Scholar**
Center for Research on Reproduction and Women's Health, Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, Philadelphia, USA

EDUCATION

INSTITUTION AND LOCATION	DEGREE	COMPLETION DATE	FIELD OF STUDY
University of Wales, School of Biosciences, U.K.	B.Sc	09/2001	Human Genetics
University of Birmingham, Medical Research Center (MRC), Medical School, U.K.	M.Sc	12/2002	Immunology and Infectious Diseases

INSTITUTION AND LOCATION	DEGREE	COMPLETION DATE	FIELD OF STUDY
Democritus University of Thrace, Health Science School, Dpt. Molecular Biology & Genetics, Greece	Ph.D	02/2008	Molecular Biology

RESEARCH INTERESTS

My research activity focuses on Molecular Biology, specializing in Bioinformatics, RNA biology, and the study of the non-coding genome, particularly in relation to cellular stress response, cancer biology, and neurodegenerative diseases such as multiple sclerosis. At the same time, I am involved in the analysis and functional interpretation of large-scale data ("omics"), with an emphasis on transcriptomics and the evolution of gene expression. My recent research extends to the study of the composition and function of small extracellular vesicles in biological fluids, such as breast milk, as well as the development of computational tools and machine learning algorithms for understanding innovative biological phenomena. The central goal of my research effort is to link molecular data with clinical applications in the diagnosis and treatment of diseases.

TEACHING ACTIVITIES

Undergraduate level «Bioinformatics», «Methods in Molecular Biology», «The World of RNA» Dept. Molecular Biology and Genetics (MBG), DUTH, Alexandroupolis, Greece.

Postgraduate level «The evolution of Gene Expression» at the MSc. Programme “Translational Research in Molecular Biology and Genetics” since 2018, Dept. Molecular Biology and Genetics, DUTH and “qPCR Data Analysis – The Gold Standard of molecular diagnosis and identification, at the MSc. Programme “Infectious Diseases and International Medicine: From Bench to Bedside”, 2018-2019, Dept. Molecular Biology and Genetics, DUTH. «Biological Databases» and «Alignment of Biological Sequences» at the MSc Programma «Applied Bioinformatics and Data Analysis» since 2020, Dept. Molecular Biology and Genetics, DUTH.

Textbook translation Participation in translation in Greek language of the textbooks *GENES VIII*, B. Lewin and *Bioinformatics and Functional Genomics*, 3rd edition (7th Chapter: Molecular Phylogenesis and Evolution), Jonathan Pevsner

Supervision 13 undergraduate (9 complete), 6 Postgraduate diploma theses (4 complete) and 3 PhD theses (1 completed)

ADMINISTRATIVE ACTIVITIES

Regular Member of the General Assembly and various internal Boards in the Department of MBG, DUTH.

PUBLICATION METRICS

- He has contributed to 22 research articles and 6 review articles in international peer-reviewed scientific journals such as: Proc Natl Acad Sci USA, Cancer Res, Clin. Cancer Res, Mol Cancer Res, Cancer Biol Ther, Cancer Lett, Scientific Reports, RNA, Expert Opin Biol Ther, Int. J. Biochem. Cell Biol., Journal of Hepatology, Atherosclerosis, Frontiers in Oncology, Bioinformatics, Nutrients, etc.
- Five articles as first author, two articles as corresponding author.
- Cumulative impact factor: 126.97, average impact factor per publication: 4.53 (recent impact factor).
- 7 articles in the last 5 years (52 citations according to Scopus).

- References: Google Scholar > 3624 (h-index: 16, i10-index: 18), Scopus > 2500 (h-index: 15).
- Organizing committee of the 16th Panhellenic Conference of the Hellenic Society for Computational Biology and Bioinformatics. October 2022, Alexandroupolis.
- Editor for the Special Issue in the International Journal of Molecular Science: "The role of lncRNAs in Stress and Disease."
- Reviewer for journals such as Cancer Letters, International Journal of Molecular Sciences, Frontiers in Oncology, Nutrients, Anticancer Research, Cancer Genomics and Proteomics, Current Issues in Molecular Biology, etc.
- Participation in the translation into Greek of the English book "GENES VIII" by B. Lewin, and 1 chapter of the book "Bioinformatics and Functional Genomics," 3rd edition (Chapter 7: Molecular Phylogeny and Evolution), Jonathan Pevsner.
- Pubmed: https://pubmed.ncbi.nlm.nih.gov/?term=Giannakakis+A&cauthor_id=37159873
- Google scholar: <https://scholar.google.com/citations?user=o-CoW3kAAAAJ&hl=en&oi=ao>
- Scopus: <https://www.scopus.com/authid/detail.uri?authorId=22034041600>

PEER-REVIEWED RESEARCH ARTICLES (IN REVERSE CHRONOLOGICAL ORDER)

APNet, an explainable sparse deep learning model to discover differentially active drivers of severe COVID-19. G. I. Gavriilidis, V. Vasileiou, S. Dimitzaki, G. Karakatsoulis, **A. Giannakakis**, G. A. Pavlopoulos, F. Psomopoulos (2025). *Bioinformatics*, vol. 41, pp. btaf063. DOI: doi.org/10.1093/bioinformatics/btaf063

D-sORF: Accurate Ab Initio Classification of Experimentally Detected Small Open Reading Frames (sORFs) Associated with Translational Machinery. N. Perdikopanis, **A. Giannakakis**, I. Kavakiotis, A. G. Hatzigeorgiou (2024). *Biology*, vol. 13, pp. 563. DOI: doi.org/10.3390/biology13080563

Analysis of Human Milk Microbiota in Northern Greece by Comparative 16S rRNA Sequencing vs. Local Dairy Animals. M. Tsifintaris, M. Sitmalidis, M. Tokamani, C. Anastasiadi, M. Georganta, I. Tsochantaridis, D. Vlachakis, P. Tsikouras, N. Nikolettos, G. P. Chrousos, R. Sandaltzopoulos, **A. Giannakakis** (2024). *Nutrients*, vol. 16, pp. 2175. DOI: doi.org/10.3390/nu16142175

KDM7A-DT induces genotoxic stress, tumorigenesis, and progression of p53 missense mutation-associated invasive breast cancer. **A. Giannakakis**, M. Tsifintaris, V. Gouzouasis, G. S. Ow, M. Y. Aau, C. Papp, A. V. Ivshina, V. A. Kuznetsov (2024). *Frontiers in Oncology*, vol. 14, pp. 1227151. DOI: 10.3389/fonc.2024.1227151

Expression and purification of human interferon alpha 2a (IFN α 2a) in the methylotrophic yeast *Pichia pastoris*. S. Chronopoulou, I. Tsochantaridis, M. Tokamani, K. D. Kokkinopliti, P. Tsomakidis, **A. Giannakakis**, A. Galanis, A. Pappa, R. Sandaltzopoulos (2023). *Protein Expression and Purification*, vol. 211, pp. 106339. DOI: doi.org/10.1016/j.pep.2023.106339.

A Multiplex PCR Melting-Curve-Analysis-Based Detection Method for the Discrimination of Five *Aspergillus* Species. M. Tokamani, E. Figgou, L. Papamichail, E. Sakka, A. Toros, A. Bouchorikou, **A. Giannakakis**, E. I. Matthaïou, R. Sandaltzopoulos (2021). *Journal of Fungi*, vol. 9, pp. 842. DOI: doi.org/10.3390/jof9080842

lncRNA NORAD is consistently detected in breastmilk exosomes and downregulated in mothers of preterm infants. N. Mourtzi, T. Sihanidou, M. Tsifintaris, E. Karamichali, A. Tasiopoulou, A. Sertedaki, M. Pesmatzoglou, A. Kapetanaki, G. Liosis, G. Baltatzis, D. Vlachakis, G. Chrousos, and **A. Giannakakis** (2021). *Int J Mol Med* 48: 216, 2021

An updated evolutionary study of the nuclear receptor protein family. L. Papageorgiou, L. Shalzi, K. Pierouli, E. Papakonstantinou, S. Manias, K. Dragoumani, N.C. Nicolaidis, **A. Giannakakis**, F. Bacopoulou, G.P. Chrousos, E. Eliopoulos, D. Vlachakis (2021). *World Academy of Sciences Journal*, vol. 3, pp. 1-8. DOI: 10.3892/wasj.2021.122

Distinctive molecular signature and activated signalling pathways in aortic smooth muscle cells of patients with myocardial infarction, T. Wongsurawat, C.C. Woo, **A. Giannakakis**, X.Y. Lin, E.S. Hwee Cheow, C.N. Lee, M. Richards, S.K. Sze, I. Nookaew, V.A. Kuznetsov, and V. Sorokin (2018). *Atherosclerosis*, vol. 271, pp. 237-244. DOI: 10.1016/j.atherosclerosis.2018.01.024

Transcriptome alterations of vascular smooth muscle cells in aortic wall of myocardial infarction patients. T. Wongsurawat, C.C. Woo, **A. Giannakakis**, X.Y. Lin, E.S. Hwee Cheow, C. Neng Lee, M. Richards, S. Kwan Sze, I. Nookaew, V.A. Kuznetsov, V. Sorokin (2018). Data in brief, vol.17, pp. 1112-1135. DOI: 10.1016/j.dib.2018.01.108

A. Giannakakis, J. Zhang, P. Jenjaroenpun, S. Nama, N. Zainolabidin, M. Y. Aau, A. A. Yarmishyn, C. Vaz, A. V. Ivshina, O. V. Grinchuk, M. Voorhoeve, L. A. Vardy, P. Sampath, V. A. Kuznetsov, I. V. Kurochkin, and E. Guccione, "Contrasting expression patterns of coding and noncoding parts of the human genome upon oxidative stress," *Sci. Rep.*, pp. 1–16, 2015.

A. Karapetsas, **A. Giannakakis**, D. Dangaj, E. Lanitis, S. Kynigopoulos, M. Lambropoulou, J.L. Tanyi, A. Galanis, S. Kakolyris, G. Trypsianis, G. Coukos, R. Sandaltzopoulos, "Over-expression of GPC6 and TMEM132D in early stage ovarian cancer correlates with CD8+ T-lymphocyte infiltration and increased patient survival." *BioMed Research International*, vol. 2015, pp. 1-9, 2015.

A. Giannakakis, A. Karapetsas, D. Dangaj, E. Lanitis, J. Tanyi, G. Coukos, and R. Sandaltzopoulos, "Overexpression of SMARCE1 is associated with CD8+ T-cell infiltration in early stage ovarian cancer," *Int. J. Biochem. Cell Biol.*, vol. 53, pp. 389–398, 2014.

A. Tan, D. H. P. Low, **A. Giannakakis**, V. Kuznetsov, C. Ferrari, E. Guccione, and A. Bertolotti, "Upregulation of chromatin modifying genes in exhausted T-cells from chronic HBV patients. *Journal of Hepatology*," vol. 60, no. 1, p. S126, 2014.

E. Beillard, S. C. Ong, **A. Giannakakis**, E. Guccione, L. A. Vardy, and P. M. Voorhoeve, "miR-Sens -a retroviral dual-luciferase reporter to detect microRNA activity in primary cells.," *RNA*, vol. 18, no. 5, pp. 1091–1100, 2012.

A. Karapetsas, **A. Giannakakis**, M. Pavlaki, M. Panayiotidis, R. Sandaltzopoulos, and A. Galanis, "Biochemical and molecular analysis of the interaction between ERK2 MAP kinase and hypoxia inducible factor-1 α ," *Int. J. Biochem. Cell Biol.*, vol. 43, no. 11, pp. 1582–1590, 2011.

L. Zhang, S. Volinia, T. Bonome, G. A. Calin, J. Greshock, N. Yang, C.-G. Liu, **A. Giannakakis**, P. Alexiou, K. Hasegawa, C. N. Johnstone, M. S. Megraw, S. Adams, H. Lassus, J. Huang, S. Kaur, S. Liang, P. Sethupathy, A. Leminen, V. A. Simossis, R. Sandaltzopoulos, Y. Naomoto, D. Katsaros, P. A. Gimotty, A. DeMichele, Q. Huang, R. Bützow, A. K. Rustgi, B. L. Weber, M. J. Birrer, A. G. Hatzigeorgiou, C. M. Croce, and G. Coukos, "Genomic and epigenetic alterations deregulate microRNA expression in human epithelial ovarian cancer," *Proc. Natl. Acad. Sci. U.S.A.*, vol. 105, no. 19, pp. 7004–7009, 2008.

A. Giannakakis, R. Sandaltzopoulos, J. Greshock, S. Liang, J. Huang, K. Hasegawa, C. Li, A. O'Brien-Jenkins, D. Katsaros, B. L. Weber, C. Simon, G. Coukos, and L. Zhang, "miR-210 links hypoxia with cell cycle regulation and is deleted in human epithelial ovarian cancer," *Cancer Biol. Ther.*, vol. 7, no. 2, pp. 255–264, 2008.

N. Yang, J. Huang, J. Greshock, S. Liang, A. Barchetti, K. Hasegawa, S. Kim, **A. Giannakakis**, C. Li, A. O'Brien-Jenkins, D. Katsaros, R. Bützow, G. Coukos, and L. Zhang, "Transcriptional regulation of PIK3CA oncogene by NF-kappaB in ovarian cancer microenvironment," *PLoS ONE*, vol. 3, no. 3, p. e1758, 2008.

L. Zhang, J. Huang, N. Yang, J. Greshock, S. Liang, K. Hasegawa, **A. Giannakakis**, N. Poulos, A. O'Brien-Jenkins, D. Katsaros, R. Bützow, B. L. Weber, and G. Coukos, "Integrative genomic analysis of phosphatidylinositol 3'-kinase family identifies PIK3R3 as a potential therapeutic target in epithelial ovarian cancer," *Clin. Cancer Res.*, vol. 13, no. 18, pp. 5314–5321, 2007.

L. Zhang, J. Huang, N. Yang, J. Greshock, M. S. Megraw, **A. Giannakakis**, S. Liang, T. L. Naylor, A. Barchetti, M. R. Ward, G. Yao, A. Medina, A. O'Brien-Jenkins, D. Katsaros, A. Hatzigeorgiou, P. A. Gimotty, B. L. Weber, and G. Coukos, "microRNAs exhibit high frequency genomic alterations in human cancer," *Proc. Natl. Acad. Sci. U.S.A.*, vol. 103, no. 24, pp. 9136–9141, 2006.

L. Zhang, J. Huang, N. Yang, S. Liang, A. Barchetti, **A. Giannakakis**, M. G. Cadungog, A. O'Brien-Jenkins, M. Massobrio, K. F. Roby, D. Katsaros, P. Gimotty, R. Bützow, B. L. Weber, and G. Coukos, "Integrative genomic analysis of protein kinase C (PKC) family identifies PKC ι as a biomarker and potential oncogene in ovarian carcinoma," *Cancer Res.*, vol. 66, no. 9, pp. 4627–4635, 2006.

REVIEWS

1. E. Papakonstantinou, K. Dragoumani, A. Mataragka, F. Bacopoulou, C. Yapijakis, N. Balatsos, K. Pissaridi, D. Ladikos, A. Eftymiadou, G. Katsaros, E. Gikas, P. Hatzis, M. Samiotaki, M. Aivaliotis, V. Megalooikonomou, **A. Giannakakis**, C. Iliopoulos, E. Bongcam-Rudloff, S. Kossida, E. Eliopoulos, G. P. Chrousos, D. Vlachakis (2024). Fingerprinting Breast Milk: Insights into Milk Exosomics. *EMBnet. Journal*, vol. 29, pp. e1048. DOI: 10.14806/ej.29.0.1048v IF: 0.4
2. V. Gouzouasis, S. Tastsoglou, **A. Giannakakis**, A. G. Hatzigeorgiou (2023). Virus-derived small RNAs and microRNAs in health and disease. *Annual Review of Biomedical Data Science*, vol. 6, pp. 275-298. DOI: 10.1146/annurev-biodatasci-122220-111429. IF: 7.0
3. L. Papageorgiou, L. Shalzi, K. Pierouli, E. Papakonstantinou, S. Manias, K. Dragoumani, N.C. Nicolaidis, **A. Giannakakis**, F. Bacopoulou, G.P. Chrousos, E. Eliopoulos and D. Vlachakis (2021). An updated evolutionary study of the nuclear receptor protein family. *World Academy of Sciences Journal*, vol. 3, pp. 1-8. DOI: 10.3892/wasj.2021.122. IF: 0.88
4. D. Vlachakis, T. Mitsis, N. Nicolaidis, A. Efthimiadou, **A. Giannakakis**, F. Bacopoulou, G.P. Chrousos (2021). Functions, pathophysiology, and current insights of exosomal endocrinology. *Molecular Medicine Reports*, vol. 23, pp 1-5. DOI: 10.3892/mmr.2020.11664. IF: 3.4
5. miRNA genetic alterations in human cancers. **A. Giannakakis**, G. Coukos, A. Hatzigeorgiou, R. Sandaltzopoulos, and L. Zhang (2007). *Expert Opin Biol Ther*, vol. 7, pp. 1375–1386. DOI: 10.1517/14712598.7.9.1375. IF: 3.6
6. Reactive oxygen species and HIF-1 signaling in cancer, A. Galanis, A. Pappa, **A. Giannakakis**, E. Lanitis, D. Dangaj, and R. Sandaltzopoulos (2008). *Cancer Lett.*, vol. 266, pp. 12–20. DOI: 10.1016/j.canlet.2008.02.028. IF: 9.1

SCIENTIFIC CONFERENCES, SEMINARS

1. 6th Analytical Metabolomics Workshop, «Untargeted Metabolomic Analysis of Small Extracellular Vesicles from Human Milk Compared to Dairy Mammals», 2025, Thessaloniki, Greece.
2. 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), «CNS recruitment of T helper 1 cells correlates with elevated CXCL10 levels in the cerebrospinal fluid of multiple sclerosis patients», 2024, Copenhagen, Denmark.
3. 23rd European Conference on Computational Biology (ECCB2024), «Biologically informed Deep Learning graph-based framework for unveiling critical lncRNAs in CLL», 2024, Turku, Finland.
4. 42nd Scientific Conference of Hellenic Society for Biological Sciences, «Development of a relational database for analyzing the cargo of animal milk-derived exosomes». 2023, Thessaloniki, Greece.
5. 72th Pan-Hellenic Conference of the Hellenic Society for Biochemistry and Molecular Biology, «Stress-induced KDM7A-DT affects DNA repair and promotes invasive breast cancer progression», 2022, Patras, Greece.
6. 15th Conference of the Hellenic Society for Computational Biology and Bioinformatics (HSCBB21), “Expression of stress induced lncRNA JHDM1D-AS1 in Breast cancer patients and cell lines”, 2021, Athens, Greece.
7. 43rd Conference of Hellenic Society of Biological Sciences (HBS), «Analysis of Human Milk Microbiome in North Greece by Comparative 16S rRNA Sequencing with Local Dairy Animals», 2024 Alexandroupolis, Greece.
8. 70th Annual conference of the Hellenic Society of Biochemistry and Molecular Biology, “Long ncRNAs consistently detected in exosomes of human breastmilk are differentially expressed in preterm compared to term childbirth mothers”, 2019, Athens Greece.
9. 6th Panhellenic Congress of the Hellenic Academy of NeuroImmunology, “Exosomal ncRNAs biomarkers and modifiers of cellular stress, potentially useful in diagnosing and treating of chronic inflammation and auto-immune/allergic disorders as cargo”, 2019, Thessaloniki, Greece.
10. Hellenic Association of Computational Biology and Bioinformatics – 17th European Conference on Computational Biology, “D-sORF: Accurate recognition of small coding ORFs ab initio”, 2018, Athens, Greece.
11. 2nd Berlin Summer School in NGS Data Analysis, “Introduction to NGS RNA-Seq Data analysis and DNA Variant Calling”, 2018, Berlin, Germany.
12. EASL: The International Liver Congress, “Upregulation of chromatin modifying genes in exhausted T cells from chronic HBV patients”, 2014, London, UK.
13. Keystone Symposia Non-Coding RNAs, “Identification and Functional Validation of Novel Non-coding RNAs as Regulators of the Cellular Stress Response to Oncogenic Insults”, Snowbird, 2012, Utah U.S.A.
14. 3rd AACR International Conference: Molecular Diagnostics in Cancer Therapeutic Development, “miRNome integrative analysis in ovarian cancer”, 2008, Philadelphia, PA. U.S.A.
15. 59th Meeting of Hellenic Society of Biochemistry and Molecular Biology, “Mir-210 is a regulator of gene expression under hypoxia and is deleted in human epithelial ovarian cancer”, 2007, Athens, Greece.
16. 22th Scientific Conference of Hellenic Society for Biological Sciences, “Functional analysis of the identified

FELLOWSHIPS & FUNDING

- 2003 – 2006** "Heracleus" Ph.D Fellowship, Principal Investigator: Prof. Raphael Sandaltzopoulos, Dpt. Molecular Biology and Genetics, Democritus University of Thrace, Greece. «Functional genomic analysis: Identification of genes that are up-regulated in specific cancer types: investigation on their importance in cancer diagnostic and therapeutic approaches»
- 2013 – 2016** JCO Career Development Award (CDA), A-STAR, Singapore, Post-doctoral Fellowship, "Identification and Functional Validation of Novel Non-Coding RNAs as Regulators of the Cellular Stress Response to Oncogenic Insults". Budget : 350,000 Singapore Dollars
- 2020-2023** Member of the research team of the project "Use of Omics Technologies for the Molecular Characterization and Enrichment of Breast Milk for Newborns" Agricultural University of Athens (AUA), and Scientific Director of the TMBG, Democritus University of Thrace. Operational Program "Competitiveness, Entrepreneurship, and Innovation" (EPAnEK), 2014-2020. Total funding: €999,545, Budget for the Democritus University of Thrace: €136,050.
- 2020-2023** Member of the research team of the project "Integration of technologies for biomedical research: multi-level analysis of biomarkers in Thrace", TMBG, DUTH, and Scientific Director of the Pilot Program (ExoMarkers): Study of secreted extracellular biomarkers in autoimmune diseases. Support for Regional Excellence, within the framework of the Operational Program "Competitiveness, Entrepreneurship, and Innovation" (EPAnEK), 2014-2020. Total funding: €2,171,950, Budget for the AG research team: €120,000
- 2020-2023** Collaborating researcher in the program "Improved Generic Polypeptide Drugs with Innovative Pharmaceutical Forms," TMBG, Democritus University of Thrace. Operational Program "Competitiveness, Entrepreneurship, and Innovation" (EPAnEK), 2014-2020. Member of the Research Team of the Department of Molecular Biology & Genetics, Democritus University of Thrace. Total funding: €999,581, Budget for the Democritus University of Thrace: €340,785
- 2023-παρόν** Collaborating researcher in the project "Application of eDNA technology for monitoring fish stocks and genetic resources in the aquatic environment of the Thracian Sea as a tool for sustainable management (ECOeDNA)". Natural Environment & Innovative Actions 2023. Funding: €200,000