BIOGRAPHICAL SKETCH

NAME: **Mylonakis, Eleftherios**

eRA COMMONS USERNAME: **EMYLONAKIS**

POSITION TITLE: Chair of Medicine, Houston Methodist Hospital

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Kapodistrian National University, Athens, Greece	M.D.	06/1990	Medicine
Kapodistrian National University, Athens, Greece	Ph.D.	06/1994	Infectious Diseases

A. Personal Statement

The Mylonakis laboratory has an interdisciplinary and translational focus, and we use a variety of tools to answer complex scientific questions. This diverse approach encompasses areas such as molecular biology, immunology, biostatistics, decision-making analysis, risk assessment, outcomes research, and cost-effectiveness studies. Our host-pathogen and antimicrobial drug discovery studies use biostatistics, whole-animal high-throughput screening, and screening by imaging to identify lead compounds and to study the fundamental molecular mechanisms that pathogens employ against a widely divergent array of metazoan hosts.

My laboratory is focused on discovering antimicrobial drugs and developing whole-animal *Caenorhabditis elegans*-based assays. We have developed several models to study host-pathogen interactions, which have led to an novel alternative to study infection and host response – invertebrate model hosts. These surrogate invertebrate hosts have proven to be important in microbial pathogenesis research as they offer a unique opportunity to identify new antimicrobial compounds and to study basic, evolutionarily conserved aspects of microbial virulence and the host response. We have identified novel virulence factors, cross-kingdom pathogen-pathogen interactions, novel antimicrobial agents, and evolutionarily conserved traits that are involved in host virulence and immune responses during infection. This approach challenges the position that pathogenesis studies should focus on the host, pathogen, or the antimicrobial compound. We have since expanded our studies to investigate antimicrobial compounds. Over the last decade, we completed a large screen of more than 90,000 compounds, and we have reported several novel scaffolds.

As the lead for this proposal, I have the experience needed for this study. My laboratory routinely performs evaluations on the mode of action, studies in mice, and *in vitro* evaluation of compounds. Overall, our work has resulted in more than 500 articles and has been cited over 38,000 times. I have co-edited several books on infectious diseases, including *Antimicrobial Drug Discovery: Emerging Strategies, Antimicrobial Stewardship: Principles and Practice*, and *Recent Advances on Model Hosts*. Within the last year, I have served as a member of study sections, and I regularly review grants for agencies from the UK, Germany, France, Austria, and other countries. We have also developed a series of collaborations that support a drug discovery program that is based on molecular and classical microbiology, biochemistry, medicinal chemistry, toxicology, animal pharmacokinetics, and efficacy to drive discoveries and understand mechanisms of action and resistance.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023-present	Chair of Medicine, Houston Methodist Hospital
2019-2023	Director, Center for Outpatient and Longitudinal Medical Research, Brown University
2019-2023	Assistant Dean for Outpatient Investigations, Warren Alpert Medical School of Brown University
2018-2023	Director, COBRE Center for Antimicrobial Resistance and Therapeutic Discovery, Miriam Hospital
2017-present	Associate Editor, ACP Journal Club (ACPJC)
2015-2013	Member and Vice Chair, New England Comparative Effectiveness Public Advisory Council
2013-2015	Member, IDWeek Program Committee (IDWPC)
2013	Member, External Advisory Committee, Harvard Institutes of Medicine
2013-2023	Member, Brown Review Committee, Translational Seed Grant Program
2012-2023	Professor of Molecular Microbiology and Immunology, Brown University

2012-2015	Consultant (Medicine Service), Massachusetts General Hospital
2012-2015	Visiting Professor, Southern Medical University, Guangzhou, P.R. China
2012-2023	Chief, Division of Infectious Diseases, Warren Alpert Medical School of Brown University
2012-2023	Charles C.J. Carpenter Professor of Infectious Disease, Warren Alpert Medical School
2012-2023	Member, RI Department of Health Infectious Diseases & Epidemiology Advisory Committee
2012-2014	Member, Brown University Kenya Program
2012-2023	ASCI representative for Brown University and Lifespan
2011-present	Member, American Society for Clinical Investigation
2010-2011	Director, Hellenic Pasteur Institute
2009-2019	Founding editor and Editor in Chief, *Virulence*
2009-2012	Associate Professor of Medicine, Harvard Medical School
2005-2009	Assistant Professor of Medicine, Harvard Medical School
2003-2009	Assistant in Medicine, Division of Infectious Diseases, Medical Services, Massachusetts General Hospital (MGH)
2002-2005	Instructor in Medicine, Harvard Medical School, Boston, MA
1999-2002	Fellow in Infectious Disease, MGH
1995-1999	Intern, Resident and Chief Medical Resident, Miriam Hospital and VAMC, Brown University, RI
1993-1995	Physician, Infectious Diseases and HIV/AIDS Unit, Evangelismos Hospital, Athens, Greece

Ad Hoc Reviewer: More than 50 journals, including ACS Infectious Diseases, Applied and Cell Host & Microbe, Circulation, Clinical Infectious Diseases, Current Genetics, JAMA, Journal of Immunology, Molecular Microbiology, NEJM, PNAS, The Journal of Infectious Diseases, and The Lancet.

Grant Reviewer: The National Science Foundation (NSF), Member of advisory panel, SDS program; Medical Research Council (MRC), UK; International Centre for Diarrheal Disease Research, Bangladesh; Albert Einstein /MMC CFAR; NIH *Ad Hoc* Reviewer; NIH/NIDCR, Member-Scientific Review Group ZDE1 RK (28), UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs); National Agency for Science, Technology and Research's and Biomedical Research Council (BMRC), Singapore; Danish Council for Independent Research; Research Fund for the Control of Infectious Disease (RFCID) and the Health and Health Services Research Fund (HHSRF), Hong Kong SAR Government, NSF CAREER award: Symbiosis Def & Self Recog, Danish Council for Independent Research Technology and Production Science, Evaluation Committee of the French National Research Agency (ANR), Member Study section: Topics in Infectious Diseases and Drug Discovery Meeting (NIAID), Member Special panel to review applications from PIs who are members of the DDR or CRFS study sections, UK Space Agency Microgravity Experiments, W. M. Keck Foundation, Austrian Federal Ministry of Education, Science and Research, NIAID Special Emphasis Panel (SEP) RFP-NIAID-DMID-NIHAI2017091, In Vitro Assessments of Antimicrobial Activity (IVAAA).

Honors

2022	Stanford's List of the World's Top 2% Scientists
2019	Fellow, American Academy of Microbiology
2019	Member, Association of American Physicians (AAP)
2014	17th annual Hygeia Award, The New England Hellenic Medical and Dental Society
2011	Partners in Excellence award in Leadership and Innovation
2010	The Oswald Avery Award, Infectious Disease Society of America (IDSA)
2005	Maxwell Finland Award for excellence in Inf. Dis. Research, Massachusetts Inf. Dis. Society
2004	Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Young Investigator Award, American Society for Microbiology
1993	Award in Chemotherapy Research, Amphiaraion Foundation, National Medical Conference, Athens, Greece

C. Contributions to Science

1. **Development of multi-host strategies and whole-animal models for the discovery and evaluation of antifungal agents and probiotics.** Invertebrate hosts fill an important niche in pathogenesis research and provide us with a unique opportunity to identify novel compounds and study basic, evolutionarily conserved aspects of virulence and host response. The use of invertebrates in automated, high-throughput *in vivo* assays can be viewed as an emerging technology related to the use of invertebrate hosts. We have leveraged *C. elegans* and *Galleria mellonella* to develop whole-animal assays that allow

screening for low molecular weight compounds and probiotics. These assays for novel antimicrobial therapies may also improve the efficiency of a primary screen in identifying quality lead compounds. By incorporating a broader array of desired compound characteristic filters into the initial screening process (e.g., potency, solubility, permeability, and toxicity), more refined hits may emerge. The assays examine some of these compound characteristics in parallel and avoid inefficiencies associated with the sequential optimization of the individual properties. These invertebrate models also permit data-driven decisions regarding the quality of a hit and eliminate preconceived biases about certain chemical classes or motifs. I served as the primary investigator or co-investigator in all of these studies.

a) Rossoni RD, de Barros PP, Mendonça IDC, Medina RP, Silva DHS, Fuchs BB, Junqueira JC, **Mylonakis E**. The Postbiotic Activity of *Lactobacillus paracasei* 28.4 Against *Candida auris*. Front Cell Infect Microbiol. 2020 Aug 4;10:397. PMCID: PMC7417517
b) Dos Santos JD, Fugisaki LRO, Medina RP, Scorzoni L, Alves MS, de Barros PP, Ribeiro FC, Fuchs BB, **Mylonakis E**, Silva DHS, Junqueira JC. *Streptococcus mutans* Secreted Products Inhibit Candida albicans Induced Oral Candidiasis. Front Microbiol. 2020 Jul 15;11:1605. PMCID: PMC7374982
c) Rossoni RD, Fuchs BB, de Barros PP, Velloso MD, Jorge AO, Junqueira JC, **Mylonakis E**. *Lactobacillus paracasei* Modulates the Immune System of *Galleria mellonella* and Protects Against *Candida albicans* Infection. PLoS One. 2017 Mar 7;12(3):e0173332. PMCID: PMC5340386
d) Coleman JJ, Komura T, Munro J, Wu MP, Busanelli RR, Koehler AN, Thomas M, Wagner FF, Holson EB, **Mylonakis E**. Activity of Caffeic Acid Phenethyl Ester in *Caenorhabditis elegans*. Future Med Chem. 2016 Nov;8(17):2033-2046. PMCID: PMC6161127

2. **Multi-host approach for the study of *Candida* spp. pathogenesis.** Many of the same pathogenesis traits are required for virulence in mammals and non-vertebrate hosts. Our results indicate that pathogens use a common, fundamental set of molecular mechanisms against a widely divergent array of metazoan hosts. We have implemented a variety of invertebrate and mammalian models to demonstrate that: 1) There are extensive similarities between infections in mammals and non-vertebrate models, including nematode and insect hosts; 2) The model microscopic nematode *C. elegans* grown on non-pathogenic yeasts has a life span similar to, or longer than, nematodes fed on the usual laboratory food source, but human pathogens kill *C. elegans*; 3) Several virulence traits that are involved in mammalian infection from a variety of pathogens are associated with *C. elegans* disease; 4) *C. elegans* assays can be used to identify novel virulence factors associated with mammalian infection, and these virulence factors provide important insights into bacterial and fungal biology; 5) *C. elegans* assays can be used to identify and study compounds with antimicrobial efficacy and multidrug resistance mechanisms; 6) During polymicrobial infection, prokaryote–eukaryote interactions modulate microbial virulence; and 7) There are evolutionarily conserved pathways for the innate sensing of pathogens, and we identified *C. elegans* receptors that (similar to their mammalian orthologues) mediate host defense. I served as the primary investigator and corresponding author in all of these studies.
   a) Lee K, **Mylonakis E**. An Intestine-Derived Neuropeptide Controls Avoidance Behavior in *Caenorhabditis elegans*. Cell Rep. 2017 Sep 5;20(10):2501-2512. doi: 10.1016/j.celrep.2017.08.053. PMID: 28877481
   b) Peleg AY, Tampakakis E, Fuchs BB, Eliopoulos GM, Moellering RC Jr, **Mylonakis E**. Prokaryote-Eukaryote Interactions Identified by Using *Caenorhabditis elegans*. Proc Natl Acad Sci USA. 2008;105(38):14585-90. PMCID: PMC2567192
   c) Pukkila-Worley R, Ausubel FM, **Mylonakis E**. *Candida albicans* Infection of *Caenorhabditis elegans* Induces Antifungal Immune Defenses. PLoS Pathog. 2011;7(6):e1002074. PMCID: PMC3121877
   d) Breger J, Fuchs BB, Aperis G, Moy TI, Ausubel FM, **Mylonakis E**. Antifungal Chemical Compounds Identified Using a *C. elegans* Pathogenicity Assay. PLoS Pathog. 2007;3(2):e18. PMCID: PMC1790726

3. **Study of novel antimicrobial compounds.** The *C. elegans*–based assays can advance drug discovery using model organisms and decrease the need for mammalian testing. Hits identified through our screens have indicated opportunities for "repurposing" drugs already used in the clinic for other therapies, and we have identified several compounds that have the potential to be used as antimicrobial agents. Evaluating these hits for efficacy, toxicity, and MOA is an important part of our work. In addition to the papers

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described above (**A. Personal Statement**), the studies below describe new chemotypes suitable for further development. I served as the primary investigator and corresponding author in all of these studies.

a) Kim W, Zhu W, Hendricks GL, Van Tyne D, Steele AD, Keohane CE, Fricke N, Conery AL, Shen S, Pan W, Lee K, Rajamuthiah R, Fuchs BB, Vlahovska PM, Wuest WM, Gilmore MS, Gao H, Ausubel FM, **Mylonakis E**. A New Class of Synthetic Retinoid Antibiotics Effective Against Bacterial Persisters. Nature 2018 Apr 5;556(7699):103-107. PMCID: PMC6462414
b) Kim W, Zou G, Hari TPA, Wilt IK, Zhu W, Galle N, Faizi HA, Hendricks GL, Tori K, Pan W, Huang X, Steele AD, Csatary EE, Dekarske MM, Rosen JL, Ribeiro NQ, Lee K, Port J, Fuchs BB, Vlahovska PM, Wuest WM, Gao H, Ausubel FM, **Mylonakis E**. A Selective Membrane-Targeting Repurposed Antibiotic with Activity Against Persistent Methicillin-Resistant *Staphylococcus aureus.* Proc Natl Acad Sci U S A. 2019 Aug 13;116(33):16529-16534. PMCID: PMC6697817
c) Kim W, Zou G, Pan W, Fricke N, Faizi HA, Kim SM, Khader R, Li S, Lee K, Escorba I, Vlahovska PM, Gao H, Ausubel FM, **Mylonakis E**. The Neutrally Charged Diarylurea Compound PQ401 Kills Antibiotic-Resistant and Antibiotic-Tolerant *Staphylococcus aureus*. mBio. 2020 Jun 30;11(3):e01140-20. PMCID: PMC7327171
d) Fuchs BB, RajaMuthiah R, Souza AC, Eatemadpour S, Rossoni RD, Santos DA, Junqueira JC, Rice LB, **Mylonakis E**. Inhibition of Bacterial and Fungal Pathogens by the Orphaned Drug Auranofin. Future Med Chem. 2016;8(2):117-32. PMCID: PMC4976847

4. **Clinical evaluation of new treatments and diagnostics.** Our efforts have contributed to clinical trials that evaluated new anti-Candida agents, such as the ReSTORE study investigating rezafungin and the MSG-10 study investigating oral ibrexafungerp, and clinical trials that developed and evaluated new diagnostics for candidiasis. I served as the primary investigator, co-investigator, or corresponding author in all of these studies.
   a) **Mylonakis E**, Zacharioudakis IM, Clancy CJ, Nguyen MH, Pappas PG. Efficacy of T2 Magnetic Resonance Assay in Monitoring Candidemia after Initiation of Antifungal Therapy: the Serial Therapeutic and Antifungal Monitoring Protocol (STAMP) Trial. J Clin Microbiol. 2018;56(4):e01756-17. PMCID: PMC5869839
   b) **Mylonakis E**, Clancy CJ, Ostrosky-Zeichner L, Garey KW, Alangaden GJ, Vazquez JA, Groeger JS, Judson MA, Vinagre YM, Heard SO, Zervou FN, Zacharioudakis IM, Kontoyiannis DP, Pappas PG. T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: a Clinical Trial. Clin Infect Dis. 2015 Mar 15;60(6):892-9. doi: 10.1093/cid/ciu959. PMID: 25586686
   c) Neely LA, Audeh M, Phung NA, Min M, Suchocki A, Plourde D, Blanco M, Demas V, Skewis LR, Anagnostou T, Coleman JJ, Wellman P, **Mylonakis E**, Lowery TJ. T2 Magnetic Resonance Enables Nanoparticle-Mediated Rapid Detection of Candidemia in Whole Blood. Sci Transl Med. 2013 Apr 24;5(182):182ra54. doi: 10.1126/scitranslmed.3005377. PMID: 23616121

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41144983/?sort=date&direction=ascending