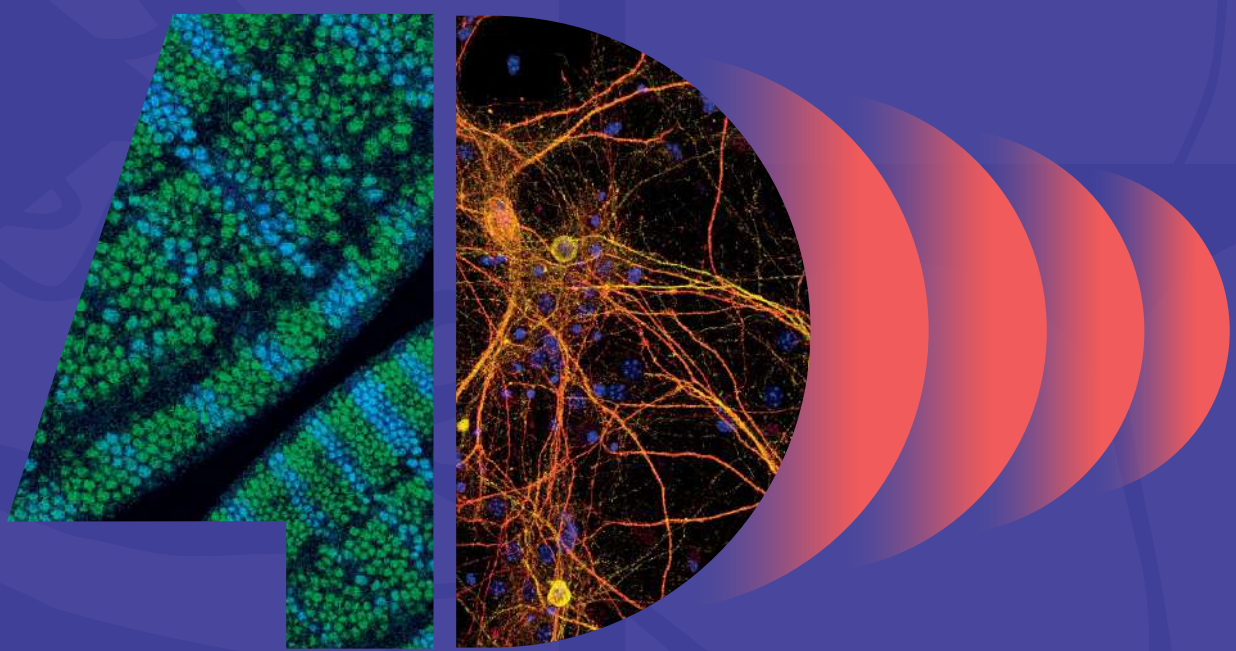
INSTITUTE OF MOLECULAR BIOLOGY
AND BIOTECHNOLOGY

BIENNIAL REPORT
2022-2023



40 YEARS | FORTH
Research • Technology • Innovation

INSTITUTE OF
MOLECULAR BIOLOGY
AND BIOTECHNOLOGY

BIENNIAL REPORT
2022-2023

40 YEARS | FORTH
Research • Technology • Innovation
FOUNDATION FOR RESEARCH AND TECHNOLOGY - HELLAS

5
Mission-Principles

6
Director's summary

9
Facts & Figures

13
Scientific Highlights

21
Timeline 2022-2023

27
IMBB Procedures

28
A short note on Mentoring

29
IMBB-Gender Equality Group (IGEG)

29
Data Management & GDPR

29
Office of Scientific Integrity at IMBB

31
IMBB Alumni Community

36
Timeline 40 years IMBB

41
Alumni said

43
Scientific Advisory Committee /
Scientific Evaluation Committee

47
Structural Biology, Biophysics-Nanobiotechnology

53
Neuroscience

61
Immunity

67
Evolution, Development & Cell Biology

73
Gene Regulation & Epigenetics

83
Plant & Plant-Microbe Biology

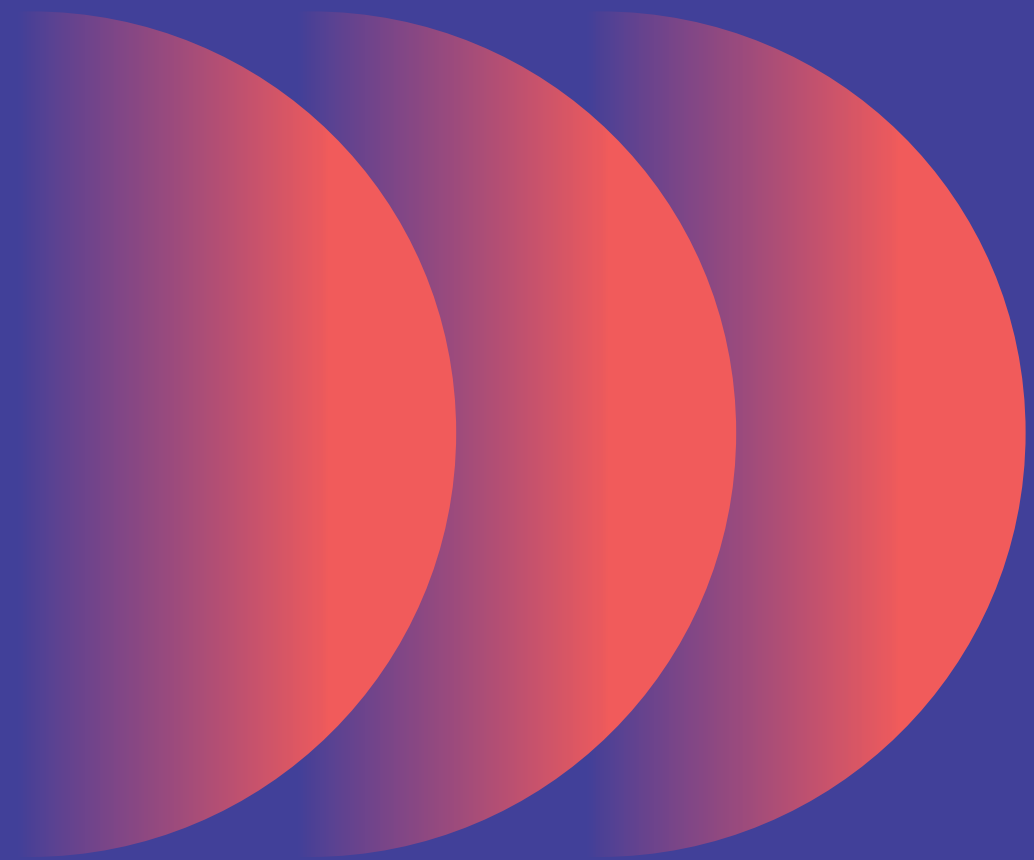
87
Insects and Vector Borne Diseases

93
Affiliated and Adjunct Faculty

95
Facilities

107
Grants

111
Administration



Support investigator driven frontier research and excellence, in a climate of freedom and independence

Mission-Principles

From the beginning of its establishment and over the years, to pursue cutting-edge research and promote scientific excellence in the field of Molecular Biology and Biotechnology, as well as exploit and translate knowledge, including the development of new technologies, innovative products and services.

Specific features:

1
Harbor a critical mass of excellent Researchers, who will contribute to an inclusive, diverse, creative environment, which operates with the highest ethical standards and enjoys a significant international visibility.

2
Pursue frontier research projects and achieve a scientific performance record, which matches the quality of leading European and US Research Centers.

3
Provide Researchers with state-of-the-art facilities and technological support.

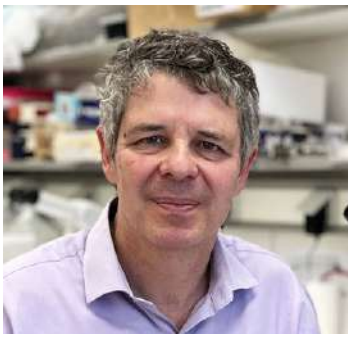
4
Provide high quality training and mentorship for PhD students and postdoctoral fellows to foster their career growth.

5
Foster diversity and creativity in research encompassing several fields of biology, through employing scientific excellence.

6
Maintain a prominent role in the multidisciplinary academic and entrepreneurial neighborhood at the FORTH campus, the University of Crete and the Heraklion University Hospital.

7
Encourage regular evaluation of the scientific performance of the Researchers by an international Scientific Advisory (Evaluation) Committee (SAC).

Director's summary



Our vision for IMBB is to continue to strive for excellent science that has been the leading principle during the 40 years of its existence. Excellence, to be implemented in a climate of scientific freedom and independence. Despite some major financial difficulties in the last period, we have been able to produce world-class science, attract prestigious grants and very talented researchers, as well as to develop impressive collaborations and networks worldwide. Many faculty members earned high-level distinctions and we substantially advanced our innovation and outreach activities.

Science

As in previous years, our research was published in peer-reviewed international scientific journals. A good percentage of the papers appeared in top scientific journals ("Scientific Highlights, p.13), indicating a promising trend during this period towards quality. IMBB Researchers have made several key discoveries with high scientific impact. Amongst them, three papers in Nature Communications: Computational models of dendrites in complex brain functions, from the group of Panayiota Poirazi and colleagues; The regulation of the three-dimensional organization of the T lymphocyte genome, by Charalambos Spilianakis and colleagues; How mitochondrial abundance modulates the rate of ageing, from the laboratory led by Nektarios Tavernarakis and colleagues. These papers not only reflect the scientific excellence of IMBB but also the different subject areas covered.

People

The scientific excellence of our members was recognized through international prizes and distinctions, such as: the election of Panayiota Poirazi as Secretary General of the Federation for European Neuroscience Societies (FENS); the election of Nektarios Tavernarakis as corresponding member of the Academy of Athens and the German Academy of Sciences Leopoldina and; the election of Electra Gizeli as EMBO member in 2023. Emmanouil Froudarakis received an ERC Starting Grant, increasing the number of IMBB's current and former ERC grantees to 9. George Dimopoulos (Johns Hopkins University) joined IMBB in 2022 as its first ERA-Chair to strengthen Vector Biology/Green Biotechnology division. Finally, Anastasios Pavlopoulos and his international team (Liangqi Frank Xie, Cleveland Clinic Foundation USA and Léo Guignard, Aix-Marseille University, France) was awarded a prestigious Research Grant from the 2023 Human Frontiers Science Program to study the cellular and molecular basis of bilaterian symmetry.

The Institute has welcomed several new group leaders. Matthieu Lavigne and Evgenia Ntini, both with a strong background in molecular biology, joined IMBB as Group Leaders in 2021. Nikos Poulakakis became a collaborating faculty member to head the Paleogenomics and Evolutionary Genetics (PEG)/ Ancient DNA laboratory. Konstantinos Stratakis with a background in genetics of human disease also joined IMBB as a Group Leader, and he is now leading DIGENIA and the Hellenic Molecular Oncology Network, under the Precision Medicine Unit. Linda Grigoraki, specialized on genetic engineering of mosquitoes, joined IMBB as Principal Staff Scientist in 2022. Michail Kotsyfakis, an expert on the biology of ticks and tick borne diseases, joined IMBB in 2023 as a Group Leader. Alexandros Pittis, a newly elected researcher (November 2023), will establish his Comparative Genomics lab at IMBB in 2024. Finally, two affiliated and adjunct faculty joined the Institute during this period: George Dialynas, a geneticist working with fungi and Paul Lasko, an eminent Drosophila geneticist. Finally, the procedure for the recruitment of two additional University of Crete collaborative researchers with excellent research profile has been initiated, and will be finalized in early 2024.

The success of the Institute is to a high degree due to the dedicated and experienced technical and administrative personnel. However, a high number of the core personnel, including very specialised scientists needed to head advanced core facilities and infrastructures, has retired or is now nearing retirement age and their replacement is not happening (no governmental positions to replace). Furthermore, we have lost many highly talented post-doctoral research associates who have chosen the safe employment in secondary education. This is a loss of critical expertise that is very hard to replace and it is a major challenge for IMBB. We continue to pursue the government to assign replacements/new positions to solve this situation, while we also explore alternative and additional solutions ("Mobility" within the government sector; more flexible short-term contracts; more efficient research management and administration procedures to reduce needs in personnel).

The years of 2022 and 2023 had also some tragic events: with great sadness and deep grief we learned of the passing away of Kyriakos Petratos, IMBB researcher, one of the pioneers and leading figures in Structural Biology/Crystallography in Greece. We and the entire scientific community was shocked by the passing away of the former IMBB Researcher and Professor at the University of Crete Tassos Economou, a Professor at the Leuven University in Belgium, a passionate scientist and excellent teacher, who made seminal discoveries in the field of protein trafficking.

Sustainable development goals

Annual financial deficits have been a very challenging issue for IMBB, particularly in 2021 and 2022 (see Facts and Figures). The central Budget from the Greek government covers only a small portion of the basic running costs, but not the dramatic increase in the cost of electricity and salaries for personnel on short-term contracts, needed to replace lost permanent positions. To ensure sustainability, a number of actions have been initiated. There has been a strong effort to encourage,

coordinate and support grant applications, with special focus on the Horizon Europe programs. This has resulted in major international grants being awarded to IMBB researchers with several million euros total funding in 2023. In addition, the successful participation in national funding instruments (GSRI Flagship and HFRI programs) have had a positive impact on the IMBB financial figures. Innovation and collaboration with private sector has been also systematically pursued in the last period. We made links with Pharma, with the aim to forge new alliances for future collaborations, some of which are currently implemented. We hope to expand our interaction with Pharma via major joint grant applications (national, EIC).

Procedures and practices to create the best environment for frontline research and development of young researchers

Since 2020, IMBB is a member of the European Alliance of research institutes advocating for excellent research (EU-Life), an initiative that begun during the Directorship of Professor Iannis Talianidis. The association with EU-Life allowed us to implement principles of transparency and meritocracy (scientific integrity, equality, communication, mentoring, data management) and act in accordance with the best current practices and procedures in Europe. In October 2022, the annual conference of EU-Life was held at IMBB, which allowed us to absorb new ideas and connect with colleagues in other Life Sciences Institutes around Europe.

A Mentoring and Career Track Scheme has been established at IMBB and it is led by the vice IMBB Director Electra Gizeli (see p.28). The scheme is in concordance with EU principles as well as the experience of the relevant EU-Life committee, with modifications stemming from the realities in Greece. The aim of the programme is to guide young scientists (Ph.D. students, post-doctoral scientists) to achieve their optimal career path. The programme has been greatly appreciated especially among the youngest researchers at IMBB.

Outreach activities

The IMBB Alumni Community was launched in 2023 with the aim to formalize and enhance contacts between our Alumni and the Institute and generate a resource that will be of value to life science in Greece as well as internationally (see p.31).

In 2023, FORTH and IMBB celebrated 40 years since their foundation. We marked this milestone with several events. An event “Precision Medicine in Modern Life” with prestigious speakers and very high participation of the general public took place in Heraklion on June 9. The major celebration of the 40-year anniversary took place on October 20 at FORTH, bringing together current members with IMBB Alumni. The event mixed scientific presentations with personal accounts and the history of IMBB. Furthermore, IMBB participated in the FORTH 40-year anniversary exhibition in Heraklion center, contributing photographs and articles highlighting our scientific history.

IMBB participated in Researchers Nights, again in 2022 and 2023, after the hiatus due to the pandemic. More than two thousand people join us during this one-night celebration of science at FORTH and it gives the opportunity to young researchers to explain their research projects to a wide and variable audience. IMBB also has a presence in outreach events such as innovation days and a significant presence in TV, radio, press and social media. We also organize several visits from local high schools.

External Scientific Evaluation

Ever since the establishment of IMBB the scientific outcome of the Institute as well as its individual group leaders have been regularly evaluated by an external Scientific Committee invited by the Institute. In 2021-22, the procedure and site visit were overseen by the General Secretariat for Research and Innovation (GSRI), Ministry of Development, and they appointed the committee members, consisting of eminent scientists from abroad (Miltos Tsiantis, Vincent Colot, Patricia Gaspar, Edith Heard, Tomas Kirchhausen, Daniel Louvard, Arthur Scherf). During a site visit, all group leaders presented their scientific progress and the committee met the Director for extensive discussions. The outcome of the evaluation was overall very positive for the achievements of the Institute. The evaluation constitutes the basis for the strategy of future developments.

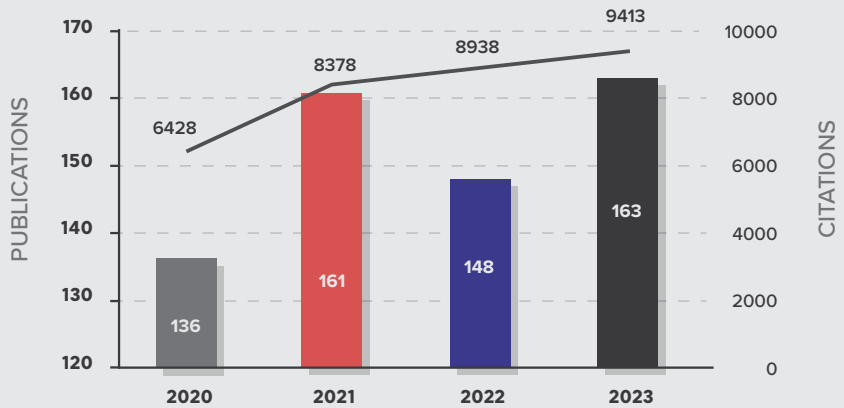
Looking to the future

We look into the future with optimism, powered by a dynamic united IMBB team, with enthusiasm, many ideas and constructive interactions among our staff and the international scientific community. Our main motivation is the commitment to excellence in science. We remain engaged in realizing our mission, to pursue cutting-edge research and innovation in the field of Molecular Biology and Biotechnology.

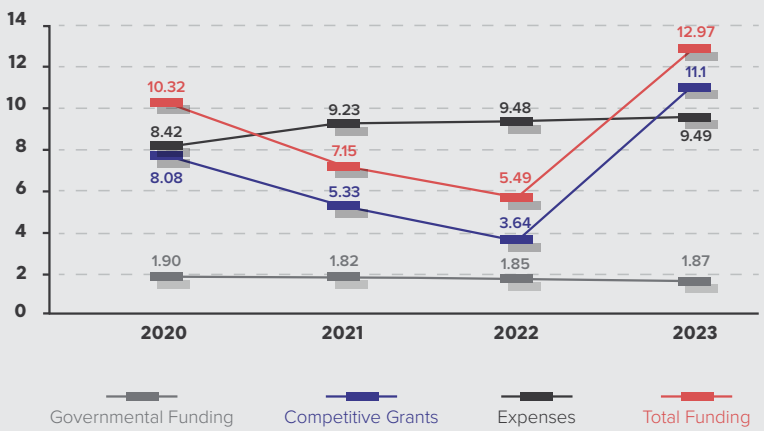
Facts & Figures

Facts & Figures

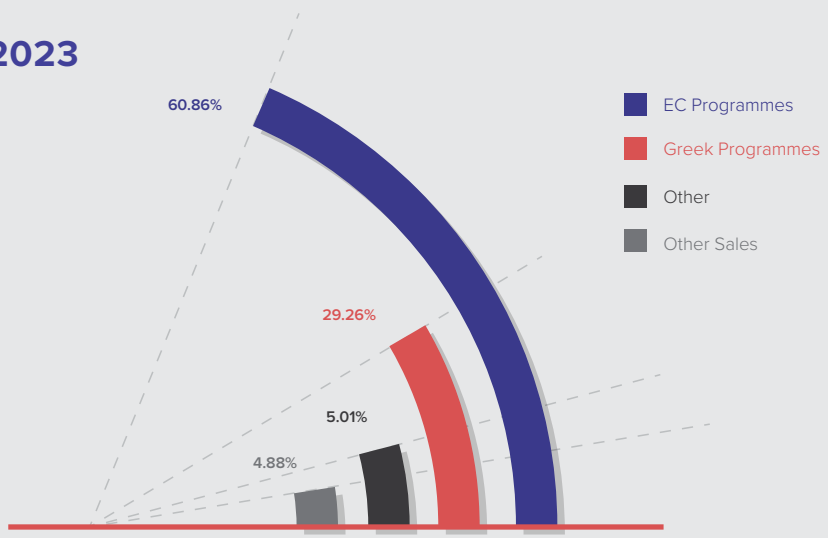
Publications & Citations



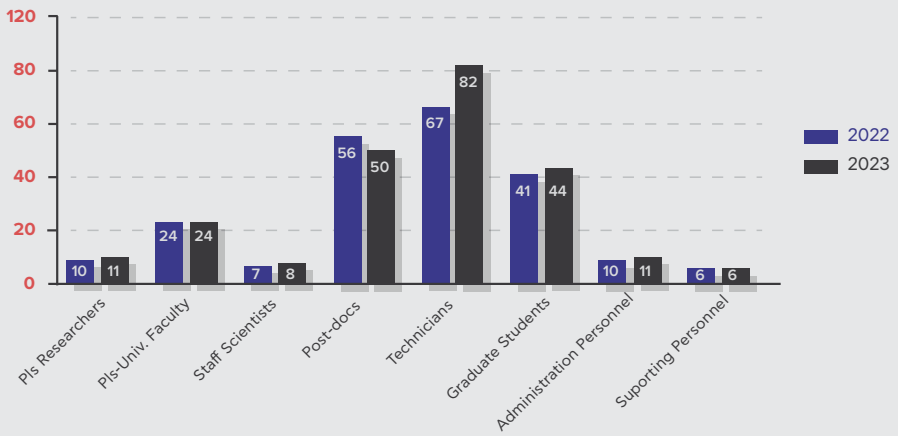
Annual Turnover



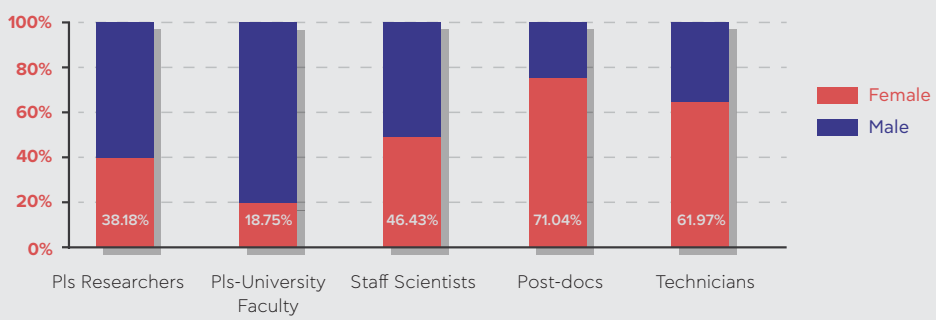
Funds & Grants 2023



IMBB Personnel in 2022 & 2023



Gender distribution of research staff 2022 - 2023



Masters & PhD degrees awarded

Scientific Highlights

Scientific highlights

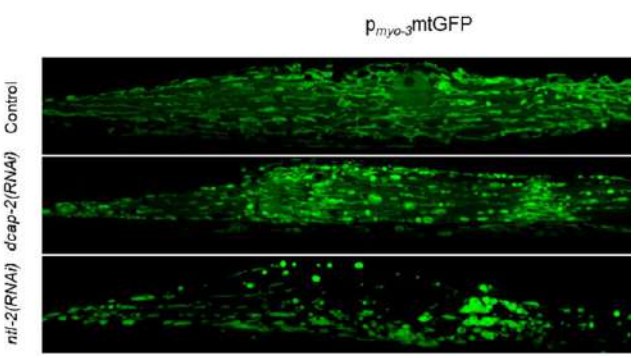
Cancer cell intrinsic mechanisms and interactions with the microenvironment shape brain tumour growth and progression to malignancy

Every year, 6 out of 100,000 people (children and adults) are diagnosed with brain, and other nervous system, cancer. Most of these patients will undergo therapeutic strategies combining surgery with radio- and chemo-therapy. However, only 33% of these patients will survive for more than 5 years. The life expectancy for the majority will be less than two years. Although there is a great research interest in neural tumours, current therapeutic strategies still remain ineffective. One of the reasons why brain tumours are hard to cure is because they are comprised of diverse cell types, both cancerous and normal. Only a subpopulation of these cells carry the combination of mutations that contributes to tumour emergence and maintenance. These cells are called cancer stem cells and it is thought that, to achieve tumour growth, they hijack developmental programs that, under physiological conditions, neural stem cells use to generate diverse cells types of neurons and glia during development and upon tissue repair. *The scientific community believes that brain tumour progression to a malignant state is the result of an intricate interplay between deregulated intrinsic mechanisms in some Cancer Stem Cells and interactions with the tumour microenvironment, including cells of the immune system that infiltrate tumour masses.* In order to study mechanisms of tumourigenesis and malignancy in the brain, IMBB researchers Dr. **Chrysanthi Voutyraki**, Dr. **Evanthia Zacharioudaki** and Professor **Christos Delidakis** used the fruitfly *D. melanogaster* where, via a simple genetic manipulation, they generated a neural stem cell derived tumour. They discovered that, as tumours progress to malignancy, developmental processes related to neuronal differentiation are shut down, whereas processes related to growth, metabolism and immunity are upregulated. By using sophisticated genetic tools, they showed that two pathways related to growth are necessary for tumour progression to malignancy. They also observed that macrophages from the host animals (the frontline soldiers of the body in the defense against invading pathogens) infiltrate tumours and resist/impede tumour growth inside their host. Live imaging revealed that macrophages engulf and consume tumour cells (a process known as phagocytosis) thus delaying tumour growth. When macrophages lack surface receptors involved in the phagocytosis of pathogens (like NimC1), they can no longer trap and engulf tumour cells thus tumours grow faster and kill their host earlier. Finally, while phagocytosis resists tumour expansion, the researchers discovered that macrophages also promote tumour growth by their natural propensity to produce reactive oxygen species (ROS) which contributes to faster host demise.

These findings contribute to a better understanding of neural tumour growth strategies and their complex interactions with their microenvironment. In the future, these insights could serve as pointers for routes to follow in studies using mammalian systems. In the long run, they could enable the design and development of novel and effective chemical or immunological approaches to target specifically the proliferation of Cancer Stem Cells in brain related tumours (e.g glioblastoma) thus improving the life expectancy of brain cancer patients.

Voutyraki C, et al. (2023) ***Proceedings of the National Academy of Science*** *120 (33): e2221601120*

A key role of mRNA metabolism determinants in ageing and disease, through the regulation of mitochondrial biogenesis and function



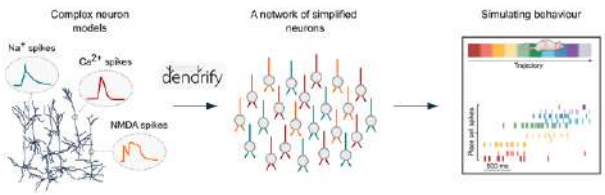
Mitochondria are specialized organelles that mainly function as energy producers, in the cells of the human body, as well as in other less complex eukaryotic organisms. Mitochondria adjust their function, morphology, and number, in response to the energy demands of cells and the whole organism. This adaptability is facilitated by complex molecular mechanisms that govern mitochondrial biogenesis, which are not fully understood. Importantly, aberrant mitochondrial biogenesis has

been linked to common age-associated diseases and severe genetic syndromes, including neurodegenerative disorders, heart failure, acute kidney injury, and type 2 diabetes.

IMBB researchers Dr. Ioanna Daskalaki, Dr. Maria Markaki and Dr. Elias Gkikas, led by Professor Nektarios Tavernarakis, discovered that specific proteins, involved in the cytoplasmic mRNA degradation pathway, play a critical role in regulating mitochondrial abundance and function, during ageing and under conditions of stress. Mitochondria display unique characteristics, resembling prokaryotes; they have their own genetic material (mitochondrial DNA), but also rely on DNA in the nucleus, which encodes the vast majority of mitochondrial proteins. While the production of mitochondrial DNA-encoded proteins is well understood, the precise regulation of nuclear DNA-encoded, mitochondrial protein synthesis remains unclear. Initially, genetic information from the nuclear DNA is transferred to the cytoplasm in the form of mRNA, which carries the required instructions for the generation of mitochondrial proteins. This dedicated protein synthesis process takes place on the outer membrane of mitochondria, and its regulation has been under intense investigation. Using the nematode *Caenorhabditis elegans*, an experimental animal that offers significant advantages for research on ageing, the IMBB researchers showed that the mRNA degradation and deadenylation complexes form distinct foci that associate closely with mitochondria, in somatic cells. The specific localization of these structures in the vicinity of mitochondria allows the regulation of mRNA transcript fate and, consequently, influences mitochondrial biogenesis during ageing and under conditions of stress. Therefore, components of these two macromolecular complexes determine the mitochondrial number and function, modulating life expectancy and stress resistance. This study provides critical insights into the complex mechanisms of ageing and highlights the importance of coordinated mRNA storage and degradation near mitochondria for the maintenance of cellular and organismal homeostasis. Furthermore, the new findings will contribute to the establishment of new biomarkers of ageing, and genetic targets for future preclinical studies, with the ultimate goal of combating diseases associated with impaired mitochondrial biogenesis and function, among others.

Daskalaki I, et al. (2023) ***The EMBO Journal*** *42: e112446*

A step closer to unraveling the secrets of the brain

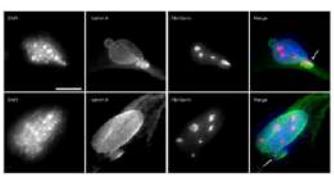


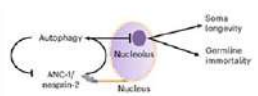
Deciphering the secrets of the brain is considered to be one of the most important scientific endeavors of the 21st century. A better understanding of the mechanisms underlying brain function will contribute both to research on the treatment of neurological diseases, as well as, on the field of Artificial Intelligence, which has become an integral part of our society. FORTH-IMBB researchers led by Dr. Panayiota Poirazi have developed innovative computational tools to unravel the role of dendrites; complex neuronal brain structures with a key role in information processing. The new software framework allows the incorporation of dendrites and their key mechanisms into large-scale neural network models. Dendrites are the branched extensions of nerve cells that morphologically resemble the branches of a tree (hence their name). Their main function is to receive information from other neurons (in the form of electrical or chemical signals) and transmit it to the main body of the cell. For decades since their discovery, their role in information processing remained unknown, due to technological limitations. But recent studies reveal that dendrites have a wealth of mechanisms that allow them to perform complex mathematical calculations independently of the main neuron. At the same time, dendrites are equally important for the plasticity of the nervous system, i.e. the ability of the brain to change and adapt to its environment. This process plays a dominant role in complex brain functions, such as learning, memory, decision making and cognition. Nowadays, although we largely understand the contribution of dendrites to the behavior of a single neuron, their implications at the level of networks or entire brain regions remain unexplored. A small number of studies correlate dendritic complexity with various cognitive markers, and dendrites are known to decline during aging or in neurodegenerative diseases such as Alzheimer's. In addition, research on AI has already benefited from the use of dendritic mechanisms as a source of inspiration for the development of new improved and more efficient algorithms. However, many open questions remain and Dr. Poirazi's team hopes that the tools they are developing will facilitate the work of the scientific community in understanding the role of dendrites in brain function. The study introduces a new software framework that allows even naive users to build neuronal models with dendrites in a simple and efficient manner, thus minimizing computational complexity. Such computational models help to elucidate the role of dendrites in complex brain functions while also facilitating their incorporation in neuromorphic devices, a type of neuro-inspired Artificial Intelligence architecture. The

new software developed allows the incorporation of important dendritic properties into neural network models. This work has important applications both in understanding brain function and in the field of Artificial Intelligence.

Pagkalos M, et al. (2023) ***Nature Communications*** *14:131*

A novel cellular mechanism that regulates ageing and fertility



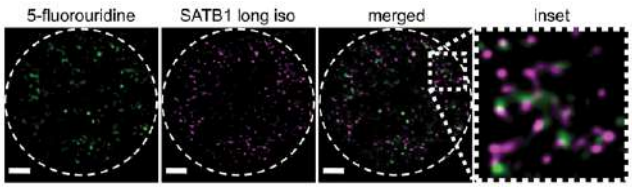


The nucleus is the central organelle of all eukaryotic cells that contains the genetic material (DNA), which determines cellular identity and function. During ageing and in cancer cells, the ultrastructure of the nucleus is dramatically altered. Moreover, progressive and pronounced deterioration of the nuclear architecture is a common and conserved feature of progeria and numerous other disorders associated with ageing. In addition, progeroid syndromes and ageing itself, are accompanied by pronounced enlargement of the nucleolus — the largest well-defined structure within the nucleus —serving as the site for generating components of the ribosome, which is the protein synthesis machine of the cell. Notably, small nucleolar size has been associated with longevity and life-extending interventions. However, the molecular and cellular mechanisms that bring about these changes have remained obscure. It is also unclear whether such alterations are simply a corollary of the ageing process and age-related pathologies, or have a causative role in progeria and senescent decline. Preservation of the nuclear ultrastructure, and recycling of nuclear material is essential for cellular and organismal homeostasis and requires the continuous and tightly regulated recycling of defective or damaged nuclear constituents. Targeting and degradation of damaged nuclear components is carried out by nucleophagy, a selective type of autophagy, which serves as a nuclear quality control mechanism. Aberrant nucleophagy has been implicated in a broad range of pathologies, including DNA damage, cancer and neurodegeneration. Nevertheless, the involvement of autophagic mechanisms in the maintenance of nuclear structure and function during ageing is unknown. A related, unresolved question relates to the signalling pathways and interventions, such as insulin/IGF1 signalling and dietary restriction, which are well-characterized modulators of lifespan, in organisms ranging from nematodes to primates. Whether, and how, these pathways interface with molecular processes that shape the nucleus, and determine nucleolar size and function during ageing, are not known. Using two experimental organisms, the nematode *Caenorhabditis elegans* and the mouse, IMBB Researchers Dr. Margarita-Elena Papandreou and Dr. Georgios Konstantinidis, led by Professor Nektarios Tavernarakis, set out to address these key questions. They report that the giant nuclear envelope, anchor protein, Nesprin-2 and its *Caenorhabditis elegans* orthologue ANC-1 are essential nucleophagy regulators. Nesprin-2/ANC-1 functions to maintain a small nucleolar size, which is a common denominator of diverse lifespan extension regimes. In addition, Nesprin-2/ANC-1 prevents nuclear shape abnormalities and accumulation of Lamin, the major structural component of the nuclear lamina. Moreover, the clearance of aberrant *C. elegans* germ cells during their differentiation, in the animal's reproductive system, the gonad, requires ANC-1-mediated nucleophagy. Remarkably, perturbation of this clearance pathway causes tumour-like structures in the *C. elegans* germline, and progressive sterility over several generations, a phenomenon of germline mortality. Similarly, genetic knockdown of Nesprin 2 in female mice causes ovarian carcinomas, indicating that the relevant molecular pathways are evolutionarily conserved, across distant phyla. Indeed, polymorphisms in the human nesprin homologue, Syne2, have been linked to ovarian infertility in women.

These findings establish that selective autophagy of nuclear material is an important determinant of somatic ageing, and germline immortality, under conditions of stress, and could be leveraged towards treating infertility in humans. The study uncovers nucleophagy as a molecular mechanism by which diverse physiological signals are integrated to impact nuclear architecture and homeostasis. Furthermore, it identifies nucleophagy as a downstream effector of low insulin/IGF1 signaling and dietary restriction on somatic ageing. Nesprin family members serve as key regulators of nucleophagy. Impairment of nuclear material recycling via nucleophagy diminishes stress resistance, undermines animal longevity and triggers progressive germline mortality. Therefore, nucleophagy is an essential soma longevity and germline immortality mechanism that promotes youthfulness and delays ageing under conditions of stress, by preserving nuclear architecture and preventing nucleolar expansion. The tight evolutionary conservation and ubiquitous expression of the regulatory factors involved, indicate that similar pathways may govern ageing in humans.

Papandreou M-E, et al. (2023) ***Nature Aging*** *3: 34–46*

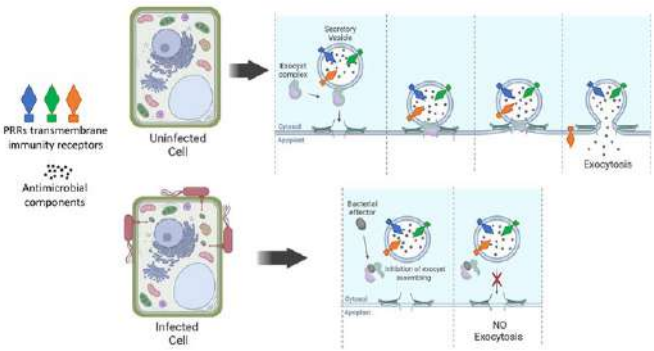
Can the three-dimensional organization of the T cell genome regulate (auto) immunity?



The research team of Professor Charalampos G. Spilianakis, at IMBB-FORTH, in collaboration with the laboratories of Christoforos Nikolaou at University of Crete, Sören Franzenburg, at Schleswing Holstein University Hospital, Kiel, and Dariusz Plewczynski at University of Warsaw, Poland investigated this question. The research team at IMBB created a T cell-specific knockout mouse that bears a deletion of the *Satb1* gene. DNA is not found naked inside our cells but rather interacts with a multitude of proteins that package and regulate it in order to fit inside the nucleus of the eukaryotic cell. The SATB1 protein binds to chromatin and regulates the three-dimensional organization of the T lymphocyte genome. This mouse model exhibits widespread autoimmunity identified by coat and skin problems, inflammation in multiple tissues and lymphoid organs (thymus and spleen). Utilizing a great number of genomic approaches, including techniques that only the research group in Crete uses nationwide and a few laboratories pan-European, the scientists involved were able to show that the SATB1 protein essentially creates gene networks in the three-dimensional space of the T lymphocyte, which expression is regulated with enormous precision. Lack of the aforementioned protein, an organizer of the T lymphocyte chromatin, leads to deregulated expression of the immune-specific genes and therefore leads to the induction of extensive inflammation and autoimmunity. The research team's next step, in the field of autoimmunity research, involves the design of highly specific small molecules to be tested for their ability to inhibit inflammation and autoimmunity, initially in a mouse model and later in humans.

Zelenka T, et al. (2022) ***Nature Communications*** *13, 6954*

Pathogenic bacteria inhibit host cell secretion to manipulate host immunity

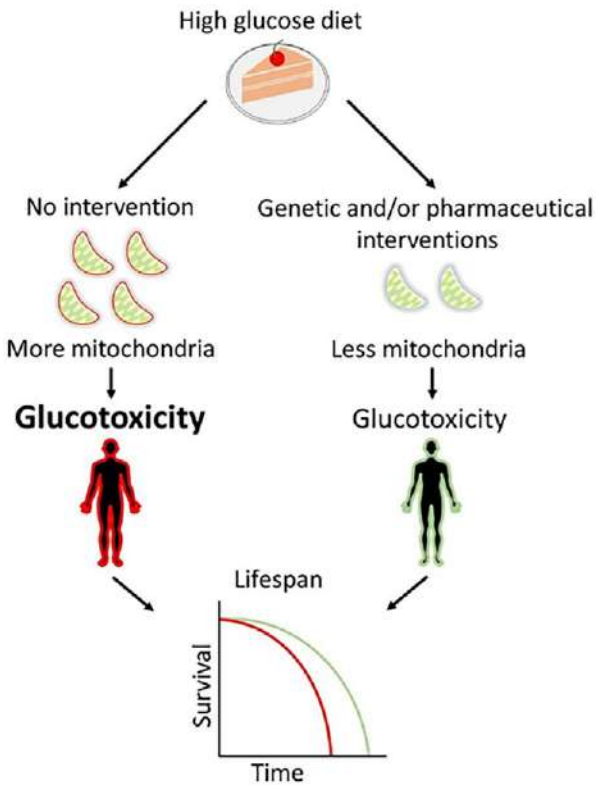


In nature, there is a constant evolutionary battle between microbes and their hosts, during which many bacteria secrete specific proteins into the host's cells, aiming to alter its physiology, while increasing pestiferous activity. Pathogenic bacteria, of both plants and animals, use common strategies to infect their hosts. During infection, the exocyst-dependent secretion machinery plays a crucial role in the host cells' defence, by secreting specific antimicrobials into the extracellular space and translocating immune receptors at the plasma membrane, in order to inhibit the growth of pathogens. The research was conducted by the research group of Professor Panagiotis F. Sarris, revealing a hitherto unknown strategy of economically important pathogenic bacteria of the *Xanthomonas* genus to inhibit the exocyst-dependent secretion mechanism of the host cells. The bacteria use a specific virulence protein (effector) that interferes with the assembly of the exocyst complex which under normal conditions, is properly assembled to translocate secretory vesicles to the cell membrane for the secretion of their content into the apoplast. In this work also collaborated the research groups of Professor Panagiotis Moschou, at the University of Crete and IMBB, Professor Jonathan DG Jones from The Sainsbury Laboratory, John Innes Centre, UK and Dr. Patrick Celie from the Dutch Cancer Institute, Amsterdam, Netherlands.

The study was carried out in the *Arabidopsis thaliana* model-plant, which appears to be an excellent model for the study of bacterial pathogenesis, and revealed that some microbes manage to inhibit the proper formation of the exocyst complex by tricking the host's immune system. It is noteworthy that exocyst inhibition by the bacterium *Xanthomonas* occurs without activating the mechanisms of the host's defence. The research team continues to study the mechanism of microbial interference to the exocyst-dependent secretion machinery and they point out that, due to the maintenance of the exocyst complex in higher eukaryotic organisms, there is evidence that this newly discovered inhibition mechanism is a strategy of many other pathogens of both plants and animals.

Michalopoulou VA, et al. (2022) ***The Plant Cell*** *34(9):3400–3424*

Metabolic reprogramming in mitochondria promotes or undermines survival and longevity

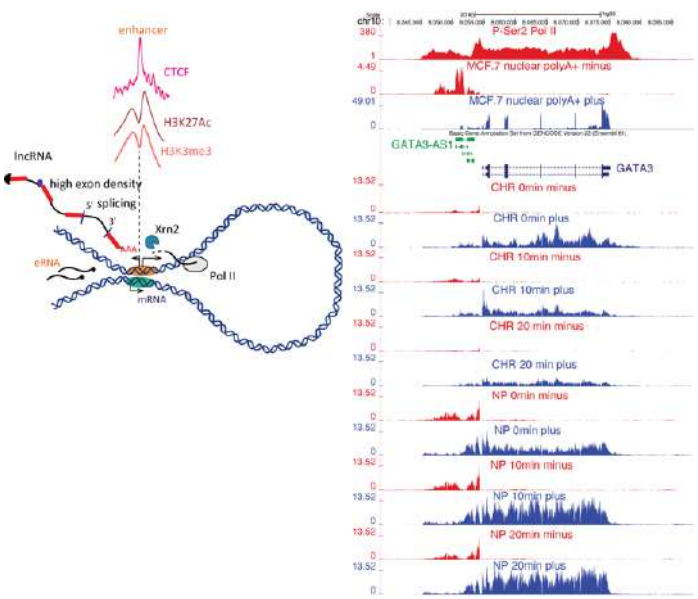


Metabolism is a complex network of biochemical reactions that allows organisms to utilize energy obtained through feeding, to grow and sustain a healthy life. Mitochondria are the main organelles for cellular energy conversions in all eukaryotic cells, and the site where the final steps of glucose breakdown take place. Importantly, alterations in metabolism critically affect the ageing process.

A study, the result of an interdisciplinary scientific collaboration between IMBB and the Institute of Chemical Engineering Sciences (ICE-HT) in Patras, now reveals that genetic or pharmacological manipulations of mitochondrial abundance in specific tissues modulate the rate of ageing. Using the nematode *Caenorhabditis elegans*, FORTH Researchers show that reduced mitochondrial abundance leads to extension of animal lifespan. Reduced mitochondrial abundance correlates with reduced reactive oxygen species production, induction of mitochondrial proteotoxic stress response mechanisms and induction of glucose uptake. Metabolic profiling of animals with reduced mitochondrial load highlights the rewiring of cellular glucose metabolism towards *de novo* biosynthesis of the amino acid serine. Interestingly, inhibition of serine production annuls the benefit that mitochondrial depletion exerts on lifespan, indicating a causative role of this biochemical pathway to longevity. Prolonged exposure to high glucose levels is known to provoke the onset of metabolic diseases, such as diabetes and obesity. Indeed, FORTH Scientists found that increased dietary glucose uptake throughout development and adulthood critically compromises lifespan. Notably, reduction of mitochondrial load ameliorates glucotoxicity and improves health during old age. These new findings provide a new framework for elucidating the mechanism whereby metabolic reprogramming contributes to longevity, and pave the way for designing tissue-specific interventions, aiming to alleviate pathologies associated with metabolic disorders.

Lionaki E, et al. (2022) ***Nature Communications 13****, 651*

Chromatin dissociation dynamics of newly transcribed RNA

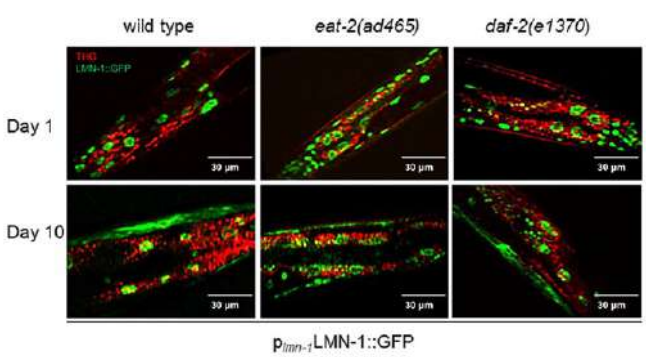


The biggest portion of the human genome is transcribed into various non-coding RNA species, some of which with regulatory potential, while most with unexplored functions. Playing an important role in regulation of gene expression, enhancers are distal regulatory elements that produce such short and long non coding RNAs (lncRNAs). lncRNAs transcribed from enhancers show high cell-type and cell state specificity, which renders them promising therapeutic targets. In order to understand features of enhancer transcription and uncover differential processing of enhancer transcribed lncRNAs, Evgenia Ntini, group leader at IMBB FORTH, established a new method (chrTT-seq) to follow nascent RNA transcripts from their transcription on chromatin to their release. This allows measuring their processing, and assessing chromatin dissociation dynamics of

newly transcribed RNA. The experimental data were used to train machine-learning models to predict distinct degrees of chromatin dissociation and identify features that are either important for fast chromatin release, or associated with slow release and chromatin tethering. The study revealed a range of chromatin dissociation rates for newly transcribed RNAs and can identify features, like splicing and distinct binding probabilities for specific RNA binding proteins, that underlie these dynamics. Furthermore, lncRNAs transcribed from enhancers and the anchor points of chromosomal loops display fast chromatin release. Thus, calling them 'enhancer-associated' does not imply that they remain 'chromatin-tethered'". The study, product of a collaboration by researchers at IMBB FORTH and Helmholtz Center Munich, describes how modeling the dynamics of chromatin dissociation of newly transcribed RNA can reveal more about the subnuclear localization, processing and functional potential of long non-coding RNAs. Overall, understanding the processing and dynamics of subcellular and subnuclear localization of lncRNAs, along with their compartment-specific RNA-binding protein interactions, can help elucidate more about their functional potential in health and disease, and drive the design of effective RNA-based therapeutic strategies.

Ntini E, et al. (2023) ***Cell Systems*** *14:906-922*

An innovative, non-invasive optical imaging technology allows monitoring of cellular lipid metabolism in live cells and organisms during ageing



Lipid droplets (LDs), the major form of fat storage in cells, are evolutionarily conserved intracellular structures that provide a pool of energy resources and building blocks for membrane synthesis and maintenance. Lipid droplets are mainly generated from the endoplasmic reticulum (ER) membranes and are localized in the cytoplasm, close to the outer nuclear membrane. However, accumulating evidence demonstrates the presence of LDs inside the cell nucleus. The nucleus is the central organelle of all eukaryotic cells that contains the genetic material (DNA), which determines cell identity and function. Despite recent advances in lipid metabolism research, the cellular mechanisms that mediate nuclear lipid deposition remain elusive.

An interdisciplinary research team from IMBB, the National and Kapodistrian University of Athens (NKUA) and the Institute of Electronic Structure & Laser (IESL), led by Professor Nektarios Tavernarakis, implemented state-of-the-art, non-linear imaging methodologies (Multi-Photon Excitation Fluorescence, Second and Third Harmonic Generation microscopy) to visualize LD deposition and distribution in cells of the simple nematode *Caenorhabditis elegans*. This non-invasive bioimaging technology can provide new insights into fundamental biological phenomena, such as, cell differentiation and function, embryogenesis, and fat metabolism during ageing, or in the context of disease. It offers improved resolution, high-contrast, increased biological sample penetration depth, and is label-free. It also permits the precise quantitative analysis and testing of specific mechanisms and biological processes.

Using this platform, the scientists discovered that lipid content progressively accumulates with age in the nuclear envelope of cells, in several tissues. Notably, such a progressive and pronounced accumulation of lipid droplets in the nucleus is a common and conserved feature of ageing and several age-associated pathologies. Importantly, genetic interventions known to delay ageing, such as low insulin signaling and dietary restriction, reduce the number and size of nuclear LDs. This suppression of lipotoxic nuclear lipid accumulation is mediated by the transcription factor HLH-30/TFEB and the triglyceride lipase ATGL-1. These findings highlight the pivotal role of lipid metabolism regulation in restraining the accumulation of LDs in the nucleus, thus preserving nuclear lipid homeostasis and organismal fitness during ageing.

Together, the findings of the study reveal a molecular mechanism regulating lipid metabolism, and highlight its critical role in preventing nuclear LD build-up, during ageing. This mechanism preserves nuclear envelope integrity and promotes nuclear homeostasis; thus, averting age-associated cellular impairment and physiological decline. The tight evolutionary conservation and ubiquitous expression of the regulatory factors involved, indicate that similar pathways may govern ageing and age-related diseases in humans.

Palikaras K, et al. (2023) ***Aging Cell*** *22:4*

Timeline 2022-2023

2022

FEBRUARY

- IMBB establishes a Collaborative Framework and 3 Agreements with Pharmaceutical Industry

MARCH

- Nektarios Tavernarakis is elected Chair of the European Institute of Innovation & Technology

MAY

- Loss of IMBB Researcher Kyriakos Petratos

- Establishment of the "Mentoring and Career Track Program" in IMBB

AUGUST

- Chair grant for "MicroBioPest" program under the leadership of Professor George Dimopoulos (Johns Hopkins, USA).

SEPTEMBER

- IMBB participates in the "2022 Researcher's night" event

JULY

- IMBB participates in FORTH «13th Scientific Retreat».
- Panayiota Poirazi is elected Secretary General of the Federation for European Neuroscience Societies (FENS)

- IMBB is awarded an ERA (European Research Area)

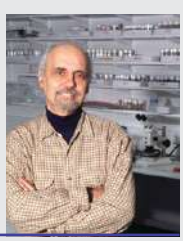
JUNE

- Completion of the IMBB Evaluation by external Scientific Evaluation Committee (SEC).

OCTOBER

- IMBB-FORTH organizes the EU-LIFE community annual meeting in Crete

- The inaugural 2022 Kafatos Lecture, organized by EMBL Alumni Relations to honor Fotis Kafatos the founder of IMBB, is held at the Cultural Conference Centre of Heraklion.



NOVEMBER

- Emmanouil Froudarakis is awarded an ERC Starting Grant

2023

JANUARY

- IMBB Alumni Community (IMBB-AC) is launched

IMBB Alumni Community

FEBRUARY

- New Researcher Michail Kotsyfakis is elected

MARCH

- IMBB researchers (Vontas, Garinis, Tavernarakis, Chamilos) coordinate 3 Flagship Actions funded by the Hellenic General Secretariat of Research and Innovation (GSRI).

Greece 2.0 NATIONAL RECOVERY AND RESILIENCE PLAN
Funded by the European Union NextGenerationEU

JULY

- Electra Gizeli is elected Member of the European Organization for Molecular Biology (EMBO)

- Nektarios Tavernarakis is elected Member of the European Academy of Sciences and Member of the German National Academy of Sciences Leopoldina
- Loss of Tassos Economou, a former IMBB Researcher and Professor University of Crete

AUGUST

- “AquaBioSens”, “UniHealth”, “NextGenBioPes” and “SoftReach”: four major EU Horizon Programs coordinated by IMBB researchers (Gizeli, Vontas, Charalampopoulos).

EU

UniHealth

AquaBioSens

NEXTGEN BIOPEST

SEPTEMBER

- IMBB participates in the “2023 Researcher’s Night” event

APRIL

- FORTH and IMBB researchers coordinate the “Greek Network on Molecular Oncology” EDIMO

MAY

- Anastasios Pavlopoulos is awarded a HFSP Research Grant
- IMBB-FORTH co-organizes and hosts the EMBO International Neuroscience Conference, entitled “Cell Biology of the Nervous System”

JUNE

- 40-years IMBB-FORTH celebration: IMBB organizes the outreach event “Precision Medicine in Modern Life”
- IMBB participates in the EU-LIFE community meeting and the “10 years EU-LIFE” anniversary conference in Lisbon, Portugal.

OCTOBER

- 40-years IMBB-FORTH celebration events:
  - **FIRST ALUMNI COMMUNITY REUNION**
  - **IMBB organizes an advanced laboratory exercise and awards High School students with excellent grades in Biology, Chemistry and Physics.**

NOVEMBER

- Emeritae Researchers Despina Alexandraki and Inga Siden-Kiamos, and administrator Mrs Georgia Houlaki are honored at a ceremony “40 years FORTH: Honoring Women in Research”
- New Researcher Alexandros Pittis is elected

DECEMBER

- IMBB participates in the two-day celebration, “40-years FORTH”.

IMBB Procedures

IMBB Procedures

A short note on Mentoring

The IMBB early-stage researchers are extremely important members of our scientific community. They perform much of the groundbreaking research, solving scientific problems and addressing challenges in a self-driven and creative way while working closely with PIs, graduate students and often undergraduates. During this intermediate-career position, postdoc researchers normally will devote their time to broaden, deepen or develop new scientific skills acquiring additional publications and becoming more competitive in the job market. However, they will also face the largest challenges for professional progression and for deciding about the next step in their career, including the delicate decision of staying in academia or pursuing a career outside of it. Within academia, the transition from a postdoc position to an independent group leader is a difficult process, primarily due to the limited number of available positions offered worldwide compared to the number of excellent post-docs. Outside academia, postdocs form a sought-after workforce of highly educated and skilled personnel suitable for a large and broad number of careers; however, sometimes they are missing some broader skills that will make them even more competitive for such positions. Unfortunately, many postdocs often ignore the multitude of career paths open to them and the options they see for their career outside academia can be quite narrow. As IMBB PIs, Group leaders and employers, we feel that it is essential to support our early researchers during their postdoc transition to the next step and assist them to build an outstanding track record suitable for the multitude of career paths open to them.

Two years ago, and with the support of our Director, I started organizing the mentoring and career track scheme (MCTS). Together with the valuable help of a group of enthusiastic IMBB colleagues (Domna Karagogeos, Eva Zacharioudaki, Inga Siden-Kiamos, Tassos Pavlopoulos, and recently Kiki Sidiropoulou), we attempted to provide a structured and formal support to IMBB postdocs regarding their future employability including diverse career paths. This was achieved through the adoption of a series of actions, all of which had a common goal: to help postdocs to decide for the career option that best suits them, both professionally and personally.

The MCTS aspires to create a multi-faceted program that will help IMBB early-stage researchers to identify personal interests, strengths and weaknesses, select suitable career opportunities and acquire the appropriate skills to effectively pursue their mid- and long- term goals.

Through three main actions, i.e., effective mentoring by a senior current or past (alumni) IMBB member during a face-to-face annual meeting; lectures given by researchers with a life sciences background and with professional careers covering a broad range of fields (academia, journalism, patenting, R&D in industry, management etc.); and, soft-skills development through courses offered by IMBB or available in the internet, IMBB postdocs were exposed for the first time to a broad range of speakers, skills and competences. All the above, inevitably, can help IMBB early researchers to open their horizons to take an informed decision on their future career path and help them to develop new skills outside the strict technical field of their expertise. Importantly, the MCTS can help postdocs to build a strong relationship with their mentor, as well as an interdisciplinary network suitable for achieving their future goals.

While we feel that the MCTS was an important initiative welcomed by the majority of the IMBB community, personally and the whole MCTS committee will continue striving for enhancing the positive outcomes of the scheme through more targeted and interactive actions, aiming to support the wellbeing of our postdocs in their current and future career lives.

Electra Gizeli
IMBB Deputy Director
MCTS Organizer

IMBB-Gender Equality Group (IGEG)

IMBB-FORTH is actively fostering a working environment in which all individuals at IMBB-FORTH are treated equally with decency, respect and fairness. It is striving to ensure an inclusive, diverse and equitable environment, where all individuals can achieve their highest potential, regardless of their gender identity and expression, sexual orientation, race, color, ethnicity, religion, age, political views, marital status, health condition or any other element that may result in discrimination. A three-member task force, known as the IMBB-Gender Equality Group (IGEG), serves as the first contact point for IMBB personnel who require more information about these issues, or wish to contribute new ideas for additional actions, or need to report complaints related to Gender Equality or any kind of inappropriate behaviour while IGEG also organizes regular scheduled events with information on these issues.

The IMBB-Gender Equality Group (IGEG):


Maria Markaki


Athanasia Papoutsi


Anastasios Pavlopoulos

IGEG is linked to EU-Life Gender Equality Working Group

EU-LIFE

Data Management & GDPR

Research Data Management involves organization, storage, maintenance and dissemination of the data generated by research projects. It is an essential activity that supports research data control, prevention of data loss, demonstration of research integrity and validation of the results, compliance with the policies and expectations of funding agencies, increasing the impact of research through sharing with and reuse of the data by other researchers.
The Research Data Management task force has developed guidelines for IMBB Policy, for data management and GDPR privacy policy.


Emmanouil Froudarakis


Emmanouil Dialynas

The task force at IMBB is linked to EU-Life Research Data Management task force.

EU-LIFE

Office of Scientific Integrity at IMBB

IMBB-FORTH is committed to promote the highest standards of scientific integrity and transparency in research and this is overseen by the Office of Scientific Integrity at IMBB. The mission of the Office is to maintain high level of scientific integrity with clear guidelines to all personnel. Focus is on the fundamental ethical principles of the Code of Conduct for Research at FORTH (Reliability; Honesty; Respect; Accountability) and related good practices in the context of Research Environment, Training, Supervision and Mentoring, Research Procedures, Safeguarding, Collaborative Working, Publication and Dissemination, Reviewing, Evaluating and Editing. It also organizes regular Training events (seminars, webinars) to disseminate good practices of scientific integrity in research. Another key mandate of the Office of Scientific Integrity is to create and maintain an optimal environment in which everyone feels safe to address potential breaches of the principles of scientific integrity.

Members of the Office of Scientific Integrity
Current members:

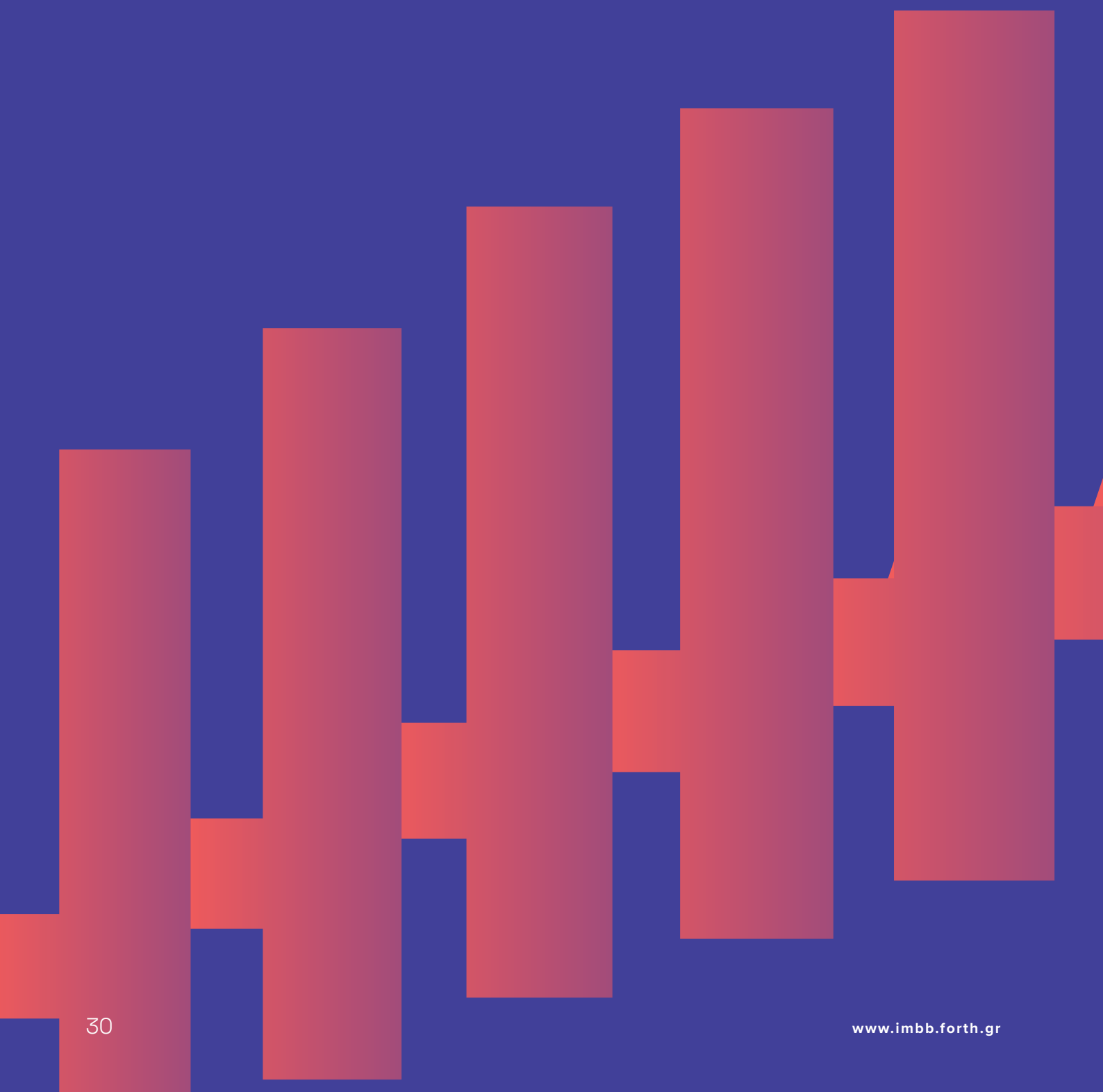

George Mavrothalassitis


Maria Monastirioti


Irini Stratidaki


Zacharenia Vlata

Past members:
Kriton Kalantidis, Inga Siden-Kiamos, Paraskevi Papakosta



IMBB Alumni Community

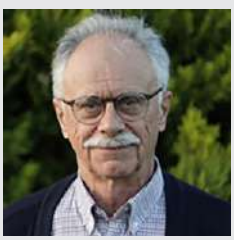
IMBB Alumni Community

In late 2022 the IMBB Alumni Community was launched. During its 40-year history IMBB has fostered many distinguished scientists who today are active in many research areas all around the world. Furthermore, the Institute has educated professionals who now work in education, in the public sector as well as in companies and private enterprises. Bringing together our former members in the Community aims to capture their contributions to the history and success of the Institute, and generate an invaluable resource for the mutual benefit of our young investigators and the scientific community, and advance life science research in Greece and abroad.

Former IMBB members were contacted by e-mail and a banner on the IMBB website and invited to join. Many accepted our invitation and today we have more than 350 members all over the world. Two channels for IMBB and the Alumni Community to interact have been established. The dedicated website contains general information as well as sections on News, Events and Career and Mentoring. Members can access a full Alumni Directory as well as collections of photos and videos. Furthermore, a Facebook group has been established where IMBB as well as alumni members can post photos, ideas or news.

IMBB Alumni Community Board

In April 2023 the Alumni Community Board was established with five members. **Babis Savakis**, who was a group leader at IMBB between 1984 to 2009, was elected chair of the board and he served a member of the organizing committee of the 40-year IMBB First Alumni Reunion. **Marirena Grigoriou** came to IMBB in 1986, as one of its first graduate students and today she is a Professor at Department of Molecular Biology & Genetics of the Democritus University of Thrace. **Maura Strigini** was a post-doc at IMBB in Domna Karagogeos group 2000-2012. At present, she is an Associate Professor at Université Jean Monnet Saint-Etienne. **Chrysoula Pitsouli** did her M.Sc. and Ph.D. degrees at IMBB with Christos Delidakis and is now Assistant Professor at the Cyprus University of Technology. Finally, Irini Topalidou did her M.Sc. and Ph.D. with George Thireos at IMBB 1997-2003 and is presently at Fred Hutch, Seattle where she has a position as Senior Scientist.



40-year IMBB First Alumni Reunion

IMBB and FORTH were established in 1983 and 2023 thus marks the 40-year anniversary. This provided an excellent opportunity to celebrate this landmark together with our alumni. On October 20, the 40-year IMBB First Alumni Reunion took place with more than a hundred of our alumni joining us at FORTH and another fifty or so on zoom. The morning session was devoted to scientific talks by distinguished alumni from IMBB: Professor Dimitris Thanos, the first graduate student at IMBB, who is now President of the Scientific Board at the Biomedical Research Foundation of the Academy of Athens, Professor Evi Soutoglou, today at University of Sussex, Professor Nikos Kyrpides at Joint Genome Institute, Lawrence Berkeley National Laboratory and finally Professor George Christofides at Imperial College. They all gave enjoyable talks with their memories from IMBB as well as overviews of their current scientific interest. Manolis Froudarakis, a researcher presently at IMBB, described his current research in neuroscience. The morning session was concluded by a brief presentation on ERC funding opportunities by Eleni Zika, European Research Council.

The afternoon session was dedicated to sharing memories of IMBB and its alumni. The history of IMBB was discussed by some of the early members of IMBB: Professors Sifis Papamatheakis, Kitsos Louis, Domna Karagogeos, and Nikos Panopoulos. They gave interesting insights into the early years of the Institute and how it established tight links with the University of Crete, both the Biology Department and the Medical School. Next, alumni from different backgrounds and diverse interests presented their experiences at IMBB, their science and their plans for the future. Many of the talks mentioned Fotis Kafatos, founder and first director of IMBB and how his legacy still lives on. This was followed by the session “In memoriam”. Despina Alexandraki had prepared a presentation of deceased IMBB members (presented by Kitsos Louis) and Sifis Papamatheakis gave a eulogy for George Thireos.

The 40-year history was collected in a graphic presentation in four sections reflecting the four decades of IMBB development (see section IMBB 40-year History Timeline). For the Alumni Community Reunion, we also collected personal photos from the groups of IMBB reminding us how the Institute has grown and changed over the years.
Alumni and current IMBB members had the opportunity to present their research or other current activities in the poster session. Alumni had also been invited to send a short video presenting themselves and these videos were shown during the meeting.

The final point on the program was live streaming with the Kafatos lecture 2023, this was given by Elena Conti who described in simple terms degradation of mRNA.
Afterwards alumni and current IMBB members as well as some invited guests were served dinner on the terrace of FORTH and a special DJ played old and new favourites.

The meeting was organized by John Vontas, Inga Siden-Kiamos, Despina Alexandraki, Maria Monastirioti, Babis Savakis and Niki Kretsovali.

Timeline 40 years IMBB

1983-1993
ESTABLISHMENT PERIOD

FUNDAMENTAL RESEARCH IN MOLECULAR BIOLOGY
focus on model organisms:
yeast, insects, mammals




DEVELOPMENT OF BIOTECHNOLOGY APPLICATIONS
plant-pathogen interactions, enzyme technology, applied immunology

1983
IMBB becomes one of the first three institutes of the newly founded **RESEARCH CENTER of CRETE.** IMBB labs are housed in the first building of UoC, near *Knossos*

Prof. F. C. Kafatos, appointed founding IMBB Director

1984
IMBB PhD program is established jointly with the Biology Department, UoC Admission of the first PhD students

1984-1987
IMBB is hosting Marine Biology and Plant Physiology guest programmes

1986
First scientific publication from IMBB (Yeast Molecular Genetics Group paper in PNAS)

1987
IMBB becomes one of the seven institutes of the **Foundation of Research and Technology-Hellas (FORTH)**

FORTH

1987-1995
Contribution of IMBB to the "Complete physical mapping of *Drosophila melanogaster genome"*

1988-1990
Research of INSECT group expands into MALARIA VECTOR biology (*Anopheles* mosquitos) and AGRICULTURAL pests (Medfly *Ceratitis capitata*)


1988
The first biotechnological products from Greece (restriction enzymes and diagnostics) are produced by the newly established MINOTECH and NIDA biotechnologies

First IMBB Retreat

1989-1996
Contribution to the "Complete Genome Sequence of *Saccharomyces cereviciae"*

First eukaryotic genome

1990-1991
Temporary re-location of some IMBB labs to *Fortetsa*

1990
Appointment of the 1st Scientific Advisory Committee (SAC) Chair: Prof. Michael Ashburner

First evaluation of IMBB achievements

1994-2003
MATURATION PERIOD

STRENGTHEN and EXPAND the STRONGEST in FUNDAMENTAL RESEARCH

QUALITY RESEARCH towards TECHNOLOGICAL INNOVATIONS of HIGH IMPACT

1994

Prof. F.C. Kafatos is appointed EMBL Director General and steps down from directorship of IMBB

Prof. George Thireos elected IMBB Director

New SAC chair: Prof. F. C. Kafatos

1995

MINOS –based transformation of Medfly *Ceratitis capitata*

1996-2000

Contribution to the "Complete Genome Sequence of *Drosophila melanogaster*"

1996

Collaboration agreement with the Department of Biology, UoC

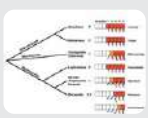
Re-location of IMBB Labs to the newly built **FORTH campus** and **University Campus-Dept. of Biology**

1997

Establishment of the Transgenic Animal Facility

1999

EVO-DEVO: A new Research Field at IMBB



1999-2002

Contribution to the "Complete Genome Sequence of *Anopheles gambiae*"

2000

Establishment of MINOS Biosystems Ltd –Spin off company

2001

IMBB, Department of Biology & Medical School of UoC, jointly establish the Inter-Institutional Graduate Program **"Master's degree (MSc) in Molecular Biology and Biomedicine"**

A new model organism in IMBB: Research with the *Caenorhabditis elegans* worm

Contribution to "Physical maps for sequencing human chromosomes"

2002

Re-location of the "Animal Facility" to new buildings at FORTH campus

2003-2004

Establishment of a new BIOINFORMATICS group, an interdisciplinary collaboration between IMBB and Institute of Computer Science (FORTH)

Timeline 40 years IMBB

2004-2013 INTO THE POST-GENOMIC ERA

HYPOTHESIS DRIVEN and POST-GENOMIC BIOLOGICAL RESEARCH

INTERDISCIPLINARITY (collaborations within FORTH)

2014-TODAY EXPANSION PERIOD

Expanding into BIOMEDICINE and TRANSLATIONAL RESEARCH

2007

Prof. F.C. Kafatos becomes the founding PRESIDENT of ERC Scientific Council

New research activities in the field of AGING are established in IMBB

2008

Establishment of "PROFI" proteomics unit

2010

Prof. Vassilis Pachnis elected IMBB Director

2012

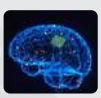
Merging of the Institute of Biomedical Research (BRI-FORTH) at Ioannina with IMBB

2013

Prof. Nektarios Tavernarakis elected IMBB Director

2014

Research expansion into FUNCTIONAL and COMPUTATIONAL NEUROSCIENCES



2016

Inauguration of the Ancient DNA Analysis Unit

2017

Prof. Iannis Talianidis elected IMBB Director

2018

Honoring F. C. Kafatos memory by naming the IMBB wing «ΦΩΤΗΣ ΚΑΦΑΤΟΣ» (FOTIS KAFATOS)

Research expansion into TRANSLASIONAL BIOMEDICINE and GREEN BIOTECHNOLOGY

2019

Foundation of two new spin-off companies

BIOPIX DNA TECHNOLOGY

Enzyquest

2020

Prof. Nektarios Tavernarakis is elected Vice President of the ERC Scientific Council

IMBB becomes Full member of EU-LIFE (alliance of top European Biomedical research Institutes)

2021

IMBB and BRI (Ioannina) are re-established as independent institutes within FORTH

Prof. John Vontas elected IMBB Director

IMBB IN NUMBERS...

2310
publications

111795
citations

> 157
in HIGH IMPACT journals

760
COMPETITIVE National, International, EU Funding

10
ERC Grants

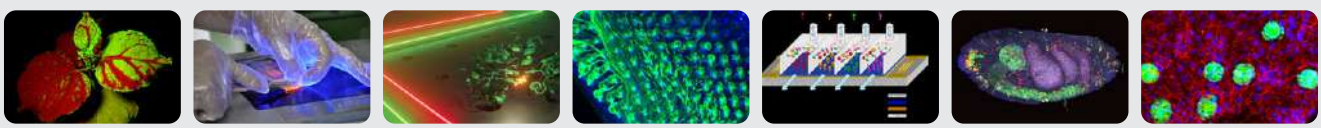
1
ERA chair

14
Patents

3
spin-offs

>300
Master

>250
PhDs



IMBB COMMUNITY TODAY

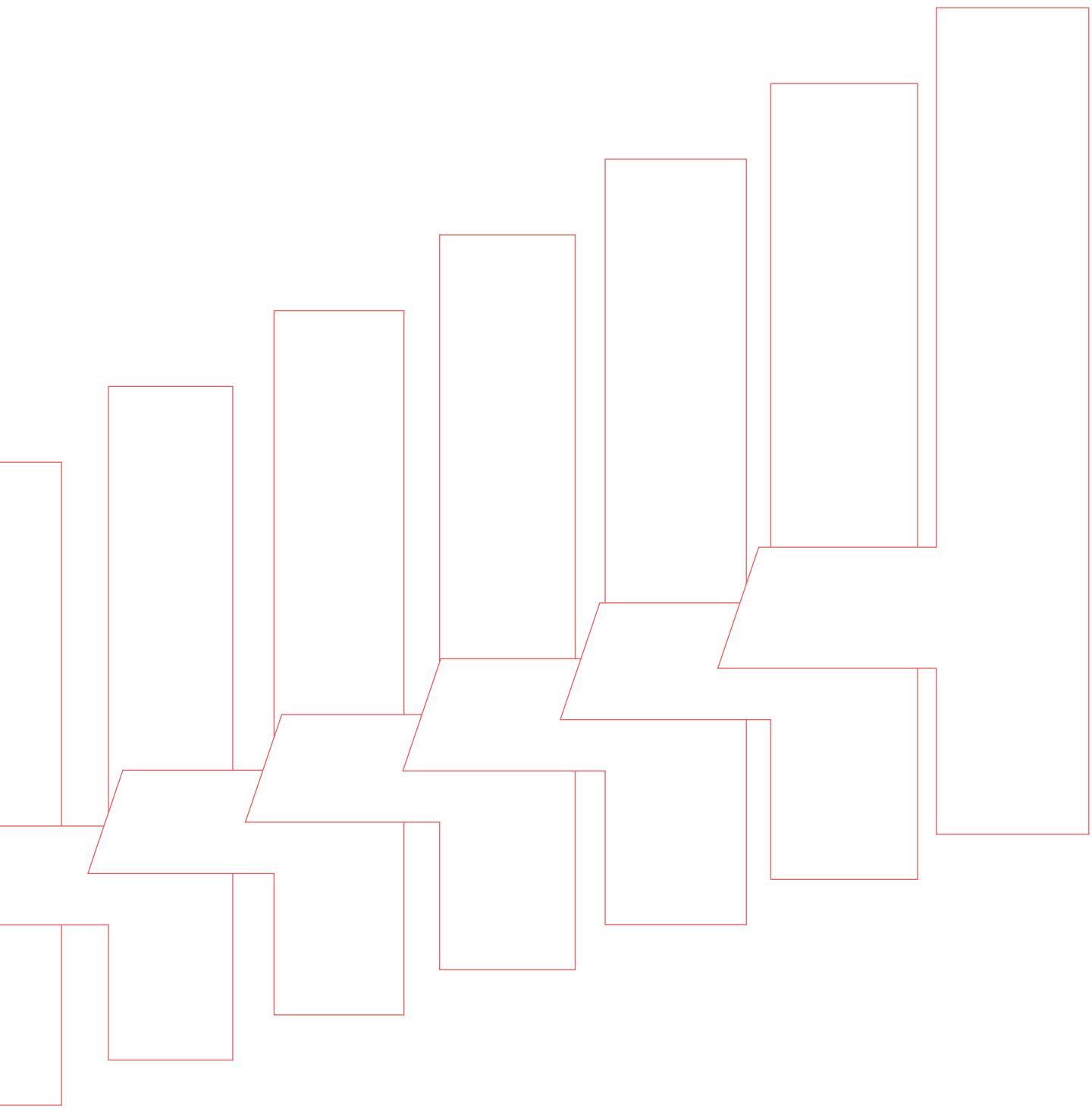
GROUP LEADERS **35**	STAFF SCIENTISTS **7**	
POST-DOC **70**	GRADUATE STUDENTS **82**	UNDERGRADUATES **>40**
TECHNICIANS **72**	ADMINISTRATION PERSONNEL **7**	SUPPORTING PERSONNEL **5**
SAC **8**	ALUMNI **342**	

IMBB 2023 AND BEYOND...

RESEARCH EXCELLENCE

SUSTAINABLE DEVELOPMENT GOALS

OPTIMUM ENVIRONMENT AND OUTREACH



Alumni said

Two aspects were characteristics of the early years of IMBB. First, the establishment of the graduate program in Molecluar Biology and Biotechnology in close collaboration with the Department of Biology and the School of Medicine. Year after year this graduate program became popular among students of other universities. Presently near all of our graduate students and post docs from that time are faculty members of US and European universities and of course they populate Greek Universities and Research Centers and a lot of them work in high ranking positions in the Pharma Industry. And secondly, the introduction for the first time in the Greek research community of an international Scientific Advisory Committee to evaluate and offer advice and useful guidelines for research and graduate programmes of IMBB.

Nicholas Moschonas (former IMBB group leader)

To my fellow alumni Please explore opportunities to reengage with the IMBB. It is very rewarding and the IMBB also produces excellent graduate students and post-docs.

George Dimopoulos (Professor, IMBB ERAchair)

Most of what I succeeded in doing in Rome and in Camerino, where I established my group, was because of IMBB, because of what I learned, not only scientifically, but on a different level also. Now I try to teach my students the way that IMBB was teaching me.

Guido Favia (former Post doc)

IMBB was what it was, a place where ambitions could be nurtured but not become a burden, a place where knowledge was appreciated but not used as a ruler to measure someone's personality. It was a place where everybody with a genuine passion for science and research, be it a group leader or a technician, could find his or her place.

Christoforos Nikolaou (former IMBB group leader)

I am overwhelmed with the exact same feeling as when I came to this building for the interview as a candidate graduate student. What really impressed me when I came here was when I saw this amazing building within the farmland. And I thought, this building was made by game changers. And what I like with this Institute is that it creates game changers.

Konstantinos Drosatos (former graduate student)

IMBB has developed a very strong sense of community. This is a unique characteristic. I have worked in nine institutions during my almost 40 years of professional life. Nowhere have I found this sense of community as in IMBB and this is a very important parameter that enhances the scientific hallmarks of the Institute and it the enriches the experience of working at IMBB. I think that starting an alumni association will strengthen this sense of community and I am very happy to have been part of IMBB and to continue to be part of IMBB in my capacity as an alumnus.

John Stroumboulis (former IMBB group leader)

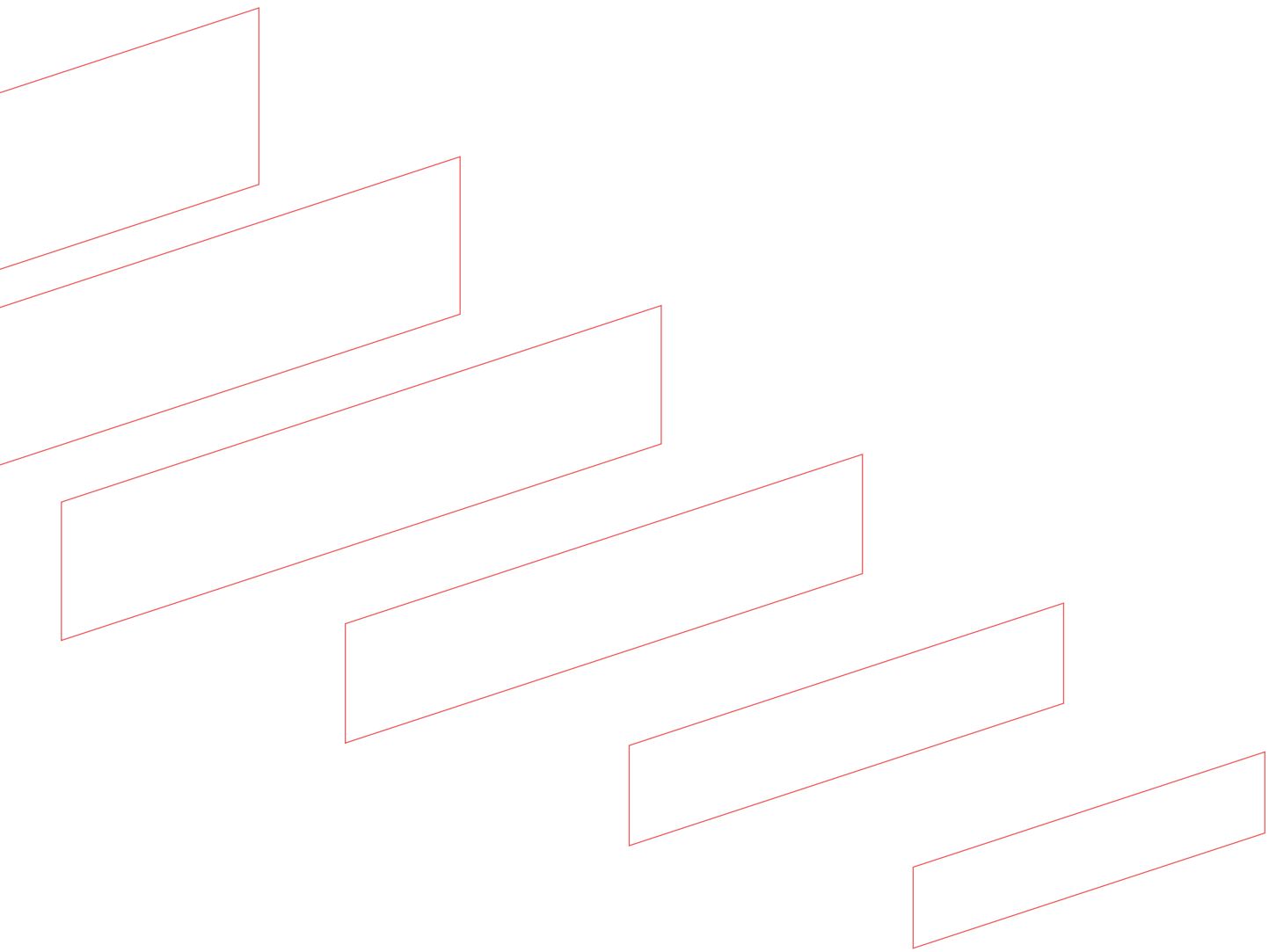
The Institute and the Post-graduate program was basically as a second family where the members were really taking care of each other, mentoring people and not only the PIs and the other people in the programme but also the technicians and the other people working behind the scenes.

Thanasis Margaritis (former Ph.D. student)

IMBB shaped my scientific thinking, shaped my career. For me IMBB means collaborative spirit. It was wonderful, those years as a graduate student. And what made most impression was the collaboration; all the laboratories were open, everyone was helping and giving us what we needed and during the breaks we did trouble shooting and supported each other.

Laskaro Zagoraiou (former Ph.D. student)

Scientific Advisory Committee / Scientific Evaluation Committee



SAC / SEC

IMBB has set up and maintains an international advisory board, which evaluates the achievements of individual researchers triennially. IMBB-SAC also provides advice in scientific management issues, development and operation of common facilities, educational program and exploitation of scientific results.
SAC is an independent board composed by the Chair (appointed by the Director and the Scientific Council of IMBB) and the Members (appointed by the Chair of SAC). Each member is appointed for a 9-years term and members rotate out in an overlapping manner to secure continuity. Current Chair of IMBB-SAC is Dr Spyros Artavanis-Tsakonas (2018-today). Previously SAC was led by Michel Ashburner and Fotis Kafatos.
In 2021 the General Secretary of Science and Innovation (GSRI) appointed Dr Miltos Tsiantis to Chair Scientific Evaluation Committee (SEC) for IMBB.

Current Members of SAC

Dr. Spyros Artavanis-Tsakonas
Chair of IMBB-SAC
Harvard Medical School, Boston, USA

Dr. Miltos Tsiantis
Chair of IMBB-SEC
Max Planck Institute for Plant Breeding Research, Cologne, Germany

Dr. Patricia Gaspar
School of Neurosciences, Paris, France

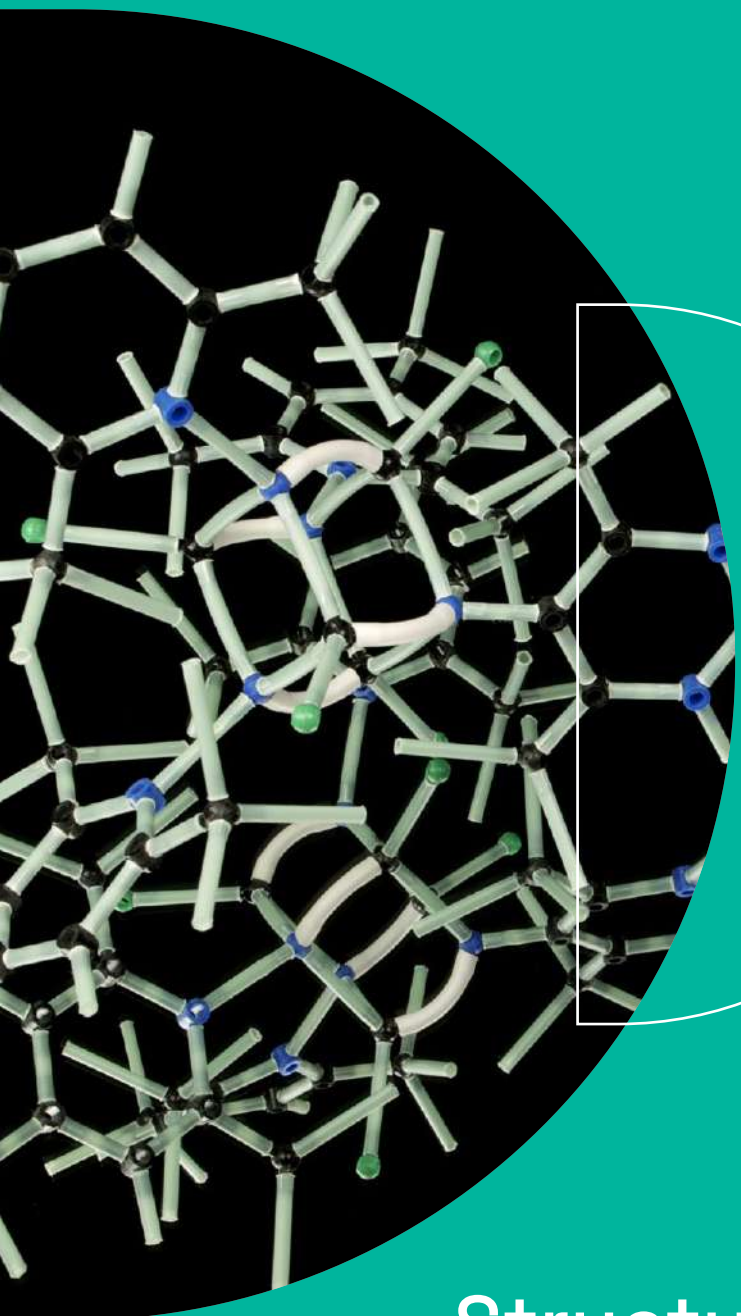
Dr. Edith Heard
Director EMBL, Heidelberg, Germany

Dr. Daniel Louvard
Institut Curie, Paris, France

Dr. Vincent Colot
Institut de Biologie de l'École Normale Supérieure, Paris, France

Dr. Tomas Kirchhausen
Boston Children's Hospital, Boston, USA

Dr. Arthur Scherf
Institut Pasteur, Paris, France



Structural Biology, Biophysics-Nanobiotechnology

Electra Gizeli

Professor - Collaborating Faculty Member

GROUP MEMBERS

Principal Staff Scientist:
Achilleas Tsortos

Post-Doctoral Researchers:
Dimitra Chronaki
Anastasia Galanopoulou
Martha Valiadi
Fred Verret

Research Assistants (MSc):
George Karolidis
Vassiliki Katidou
Aggelos Ntimtsas
Vaia Tsiakalou

Lab Manager:
Maria Megariti
MSc

PhD students:
Katherine Hartle-Mougiou
Stelios Grammatikos

MSc students:
Vassiliki Chatzimichali
Giannis Markopoulos
Zenia Viskadouraki

Undergraduate thesis students:
Triantafyllia Giora
Orestis Kokolakis

Visiting Researchers:
Dr. Ian Bothka
UCLH, May 2023
Prof. Angelantonio Minafra
CNR, Sept. 2023

BIOSENSORS

Summary

Our multidisciplinary activities combine novel research with technological advancements in the fields of molecular biology, biosensors, nano-biotechnology and biomedical engineering. Innovation for the transfer of new concepts from the lab to the society has been a constant inspiration in the group. We strive to provide rapid, cost-effective solutions for infectious disease testing, alleviating patients and contributing to global challenges such as HIV, influenza and other emerging diseases testing in the developed and developing countries. Addressing molecular diagnostics within One-Health concept is another central theme of our lab. Finally, we continue our interest in biophysics by using acoustic biosensors to study the mechanism of membrane-bound interactions.

Current aims

We continue our work on the development of robust and sensitive isothermal amplification assays and methodologies, experimenting with LAMP, RPA and CRISPR/Cas assays methodologies. We are currently working to the following:

- Contribute towards the WHO goal to have 95% of people living with HIV (currently 39M worldwide) diagnosed by 2030 using our novel lateral flow molecular assay and reader for detection and (semi)quantification
- Expand our work on nanoparticles (NPs)for nucleic acids detection using as well carbon nanoclusters
- Focus on delivering diagnostic solutions and surveillance tools for the better preparedness of the world to address future emerging diseases and pandemics

Progress in 2022-2023

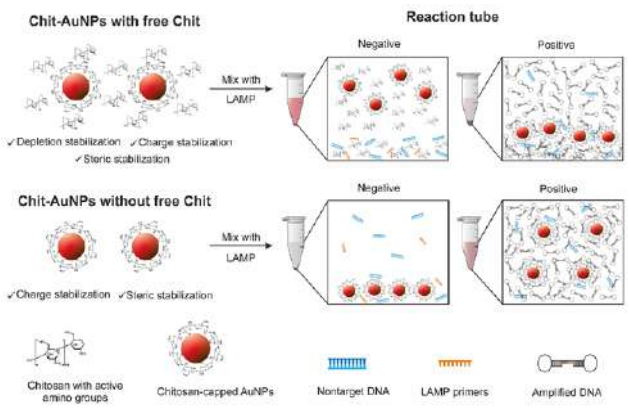
i) Our biophysical acoustic studies produced valuable insight on how the early endosome antigen 1 (EEA1) protein binds to endosome-mimicking membranes and on the structure of EEA1 on the membrane (HFSP)

ii) Green-synthesized AuNPs, synthesized in the lab and capped with a chitosan layer were demonstrated to be able to detect 1-5 viral copies in 20% saliva, a remarkable sensitivity for naked-eye colorimetric detection (EC-H2020 “TechOceanSens”)

iii) We participated in field studies where our novel assays and platforms for HIV and influenza testing were evaluated under real-world conditions (EC-FETOPEN “FREE@POC”)

iv) We designed, fabricated and validated two patented portable 3D-printed platforms for genetic and protein testing outside a dedicated lab (“FREE@POC”)

v) Through our participation as the coordinator of EU-funded RIA project “IRIS-COV”, we contributed to the final development and IVD-validation of three new products, exploited by IMBB spin off “BIOPIX DNA TECHNOLOGY” (EC-H2020 “IRIS-COV”)



Mechanism of colorimetric naked-eye detection of isothermally amplified DNA (here Salmonella) using chitosan capped AuNPs. Fine tuning of the stabilization/destabilization forces in the solution can result in the detection of 1-5 copies/reaction in the presence of a crude sample (saliva).

Other activities

- Electra Gizeli was elected member of the European Molecular Biology Organization (EMBO) (2023)
- Martha Valiadi secured competitive EC-funding for the lab under HORIZON–Zero Pollution R&I action call (“AquaBioSens”) (2023)
- Anastasia Galanopoulou and Electra Gizeli visited the African Health Research Institute (AHRI) in S. Africa to organize a pilot clinical validation study of our newly developed instrument-free methodology
- Electra Gizeli was elected member of the Scientific Advisory Board of the Global Health European and Developing Countries Clinical Trial Partnership (EDCTP3), to advise EC on startegies for diagnostics and innovation in Sub-Saharan Africa

Web page https://www.gizeligroup.eu/

Publications

Grammatikos S, et al. (2023) Naked-Eye Detection of LAMP-Produced Nucleic Acids in Saliva using Chitosan-capped AuNPs in a Single-Tube Assay. **Analytical Chemistry** 95 (50):18514-18521 doi.org/10.1021/acs.analchem.3c03878 (PMC10733902)

Papadakis* G, et al. (2022) Real-time colorimetric LAMP methodology for quantitative colorimetric nucleic acids detection at the point-of-care. **Scientific Reports** 12: 3775 doi.org/10.1038/s41598-022-06632-7

Naoumi N, et al. (2022) Acoustic array biochip combined with allele-specific PCR for multiple cancer mutation analysis in tissue and liquid biopsy **ACS Sensors** 7: 495-503 doi.org/10.1021/acssensors.1c02245

Giorgos Gouridis
Principal Researcher (B)

GROUP MEMBERS

Senior research personnel:
Mary Providaki

Postdoctoral researchers:
Eleni Makraki
Yusran A. Muthahari
former

PhD students:
Chara Sarafoglou
Ruixue Xu
former

DYNAMIC STRUCTURAL BIOLOGY

Summary

The aim of our group to understand life and protein evolvability at the molecular level is persuaded by studying folding and native state dynamics of proteins. Our lab's holy grail is to: (i) Find the key structural elements and understand how such modulate the depth of the energy valleys of the folding funnel, (ii) Understand how such elements modulate the enthalpic-entropic factors to by-pass the transition barriers and ultimately (iii) How these elements vary during evolution to confer distinct functions and specificities.

Our recent research uncovered the remarkable modularity of proteins. During evolution, a conserved structural core can acquire secondary structural elements, alike lego bricks added on a core-board, over time. Such elements represent allosteric modules that enable the statistical thermodynamic coupling and by that orchestrate multi-tier structural dynamics. In doing so, these elements diversify the function and specificity of the core and resolve evolutionary tradeoffs.

Current aims

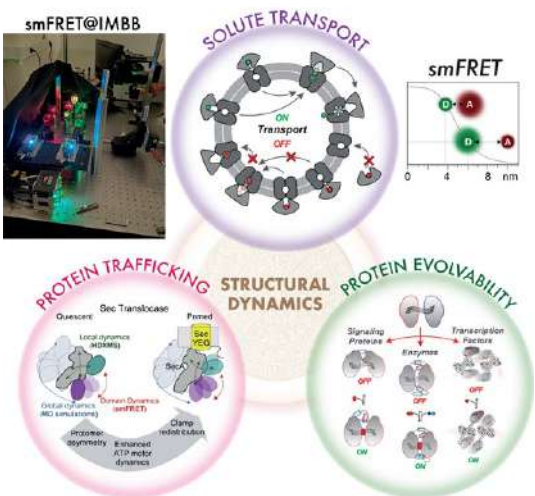
Our research line is based on a **3-pronged approach**:
(A) Fundamental research; **(B)** Drug development and **(C)** Tech transfer / High-throughput screening. For this, we are focusing on human Ras signaling proteins, Nuclear Receptors (NRs) and bacterial bilobed proteins. Ras regulate many signaling pathways, being responsible for 30% of human cancers. NRs (Nurr1, RxR) undergo tertiary and quaternary dynamics to regulate transcription and constitute more that 15% of current drug targets as involved in neurodegenerative disorders and cancer. Bilobed proteins are responsible for transcriptional regulation (e.g. LysR transcription factors), pathogenicity (e.g. FbpA) or mediating the uptake of nutrients (e.g. MalE). Our vision is by establishing and developing biophysical tools (smFRET, HDX-MS, etc.); to create a unique hub in Greece for modern dynamic structural biology related research. We are grateful to the groups of Prof. Cordes (LMU-Germany), Prof. Dömling (Olomouc-Czech Republic), Prof. Kokkinidis (IMBB-Greece) and Dr. Papanastasiou (Broad Institute-US); for gifts, material-and expertise-transfer via which we are materializing our vision.

Progress in 2022-2023

i) In this biannual period, we established the Dynamic Structural Biology laboratory at IMBB and developed multiple biophysical cross-disciplinary approaches for protein-related research. (a) We constructed in collaboration with the group headed by Dr. Zacharakis (IESL-FORTH) a custom-made confocal microscope for single-molecule FRET experiments. (b) We established HDX-MS expertise at the proteomics facility of IMBB in collaboration with Dr. Papanastasiou (Broad Institute-US). (c) We established advanced machine learning procedures for the analysis of complex biophysical data in collaboration with the group headed by Dr. Pantazis (IACM-FORTH). Currently, we are developing sophisticated statistical approaches for the analysis of protein structures.

ii) We elucidated the role of structural dynamics in: (A) Protein trafficking (Krishnamurthy et al, Structure; Krishnamurthy et al, Cell Rep) by probing the preprotein translocase (~300 kDa membrane complex) at work at the single molecule level. (B) Solute transport (Ploetz et al, Open biology) by probing distinctively the structural dynamic of each of the two substrate binding domains of an ABC importer with smFRET. (C) Protein evolvability (Gouridis et al, PNAS; Muthahari et al, under review) by monitoring the multi-tier structural dynamics of proteins harboring a highly evolvable bilobed structural scaffold. In doing so, we were able to decrypt the origin and resolution of life-history tradeoffs.

iii) We also participated in a study aiming to understand the involvement of an ABC transporter in insecticide toxicity (Kefi et al, PLoS Pathog). For this, we performed homology modelling and in silico docking experiments.



Other activities

- Obtained 2 multi-PI grants (Emblematic Action and FORTH Synergy grants)
- Two lab researchers that obtained their PhDs are currently post-doctoral researchers at top universities (OIST research center/Japan, Yale school of Medicine/US)
- One post-doctoral researcher obtained MSCA funding

Web page https://www.imbb.forth.gr/imbb-people/en/gouridis-research

Publications

Krishnamurthy S, et al. (2022) Preproteins couple the intrinsic dynamics of SecA to its ATPase cycle to translocate via a catch and release mechanism. **Cell Rep**. 38 (6): 110346

Gouridis G, et al. (2021) Structural dynamics in the evolution of a bilobed protein scaffold. **PNAS** 118(49): e2026165118

Krishnamurthy S, (2021) A nexus of intrinsic dynamics underlies translocase priming. **Structure** 29:846-858

Michael Kokkinidis

Professor Emeritus - Collaborating Faculty Member

GROUP MEMBERS

Post-Doctoral Researchers:
Dr. K. Kefala
Dr. E. Mylonas

PhD students:
A. Molfetas
A. Lemonakis

Research Assistants:
D. Kotsifaki
M. Providaki

PROTEIN STRUCTURE/CRYSTALLOGRAPHY

Summary

We have used Structural Biology techniques to develop a detailed and comprehensive understanding of protein folding and its dependence on protein sequence and we were able to develop rational protein design approaches suitable for the engineering of novel proteins and bio-inspired materials. The have a wide range of health and materials science applications. We discovered and explored in depth the exciting mechanism of autocatalytic hydroxylation of the proline Cα atom, the smallest possible post-translational modification of protein molecules. This Pro to 2-hydroxyproline (2-Hyp) conversion has potentially far-reaching implications in Health and Biotechnology; our recent insights reveal that it could be far more widespread than originally thought. In addition, we performed structural studies on several enzymes (e.g. the human glutamate dehydrogenase 2, hGDH2) that are relevant to human health and drugs development.

Current aims

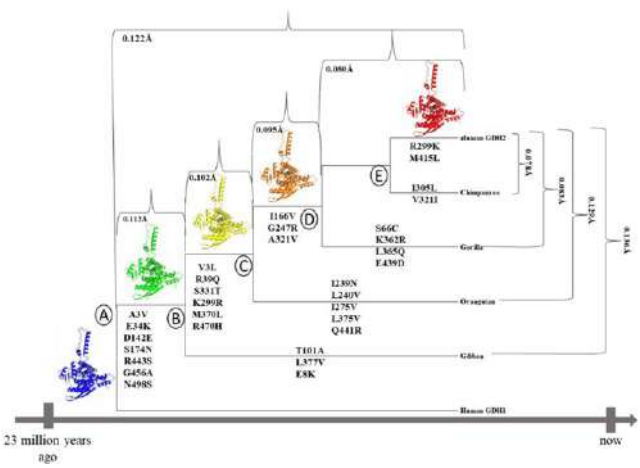
- Protein folding studies for α-helical tertiary motifs, using the approach of sequence reversal, so as to explore vast regions of sequence space that has not yet sampled by known natural protein sequences.
- Understanding the mechanism and extent of autocatalytic Cα hydroxylation and specifically: a) Structural/ functional implications b) Evolutionary aspects of self-hydroxylation (e.g. pseudoenzymes from the carbohydrate esterase family CE4 that have evolved towards inactive forms for the deacetylation reaction). c) Establishment of potential links between Cα hydroxylation and human diseases, e.g. Gly Cα hydroxylation vs. cancer proliferation.
- Structure-function studies on enzymes that are important to human health, e.g. hGDH2, which provide insights to human brain evolution and potentially opens new avenues for drug design/ cancer therapeutics.

Progress in 2022-2023

i) Amino acid sequence reversal was employed for engineered α-helical bundles and the structural/ physicochemical properties of their retro-proteins were characterized, revealing factors that affect protein 'foldability' for poorly characterized regions of the protein sequence space.

ii) Modes of the autocatalytic Cα hydroxylation of Gly were analysed, revealing the presence of single- and double- hydroxylation events, as predicted by us on the basis of the chemical properties of Gly residues. Self-hydroxylation mechanisms were also studied for the CE4 enzyme family of bacterial pathogens where "pseudoenzymes" have evolved with altered enzymatic properties. To our surprise, Cα hydroxylation of Gly residues in model system proteins was found to be far more widespread than originally believed, although the highest occurrence of this modification is associated with the active site of the enzyme. The exact chemical/ enzymatic nature of the self-hydroxylation mechanism in proteins is still poorly understood.

iii) Based on our crystallographic analysis of the human glutamate dehydrogenase 2, we created a structure-based model for the evolutionary adaptations of this critical enzyme in modern apes and humans, over the course of the last 23 million years.



Phylogenetic tree for experimental (human) or predicted (great apes) GLUD2 structures, based on sequences encoding the mature peptide. On its branches, the amino acid substitutions that led to the current GDH2 proteins in great apes are depicted. Numbers refer to the RMSD values for each comparison.

Other activities

- Guest editor of International Journal of Molecular Sciences.

Web page www.imbb.forth.gr/kokkinidis

Publications

Arnittali M, et al. (2023) Structure of amino acid sequence-reversed wtRop protein: insights from atomistic molecular dynamics simulations. **Journal of Biomolecular Structure and Dynamics** 6:1-15 doi: 10.1080/07391102.2023.2252903

Litso I, et al. (2023) Structural Evolution of Primate Glutamate Dehydrogenase 2 as Revealed by In Silico Predictions and Experimentally Determined Structures. **Biomolecules** 14:22. doi.org/10.3390/biom14010022

Makraki E, et al, (2023) Probing the conformational changes of in vivo overexpressed cell cycle regulator 6S ncRNA. **Front. Mol. Biosci**. 10:1219668. doi:10.3389/fmolb.2023.1219668

Achilleas Tsortos
Principal Staff Scientist - Gizeli Lab

MOLECULAR BIOPHYSICS & BIOSENSORS

I am a Biophysicist and member of the “Biosensors Laboratory” (Professor E. Gizeli).
My research interests (experimental & theoretical) are in the areas of

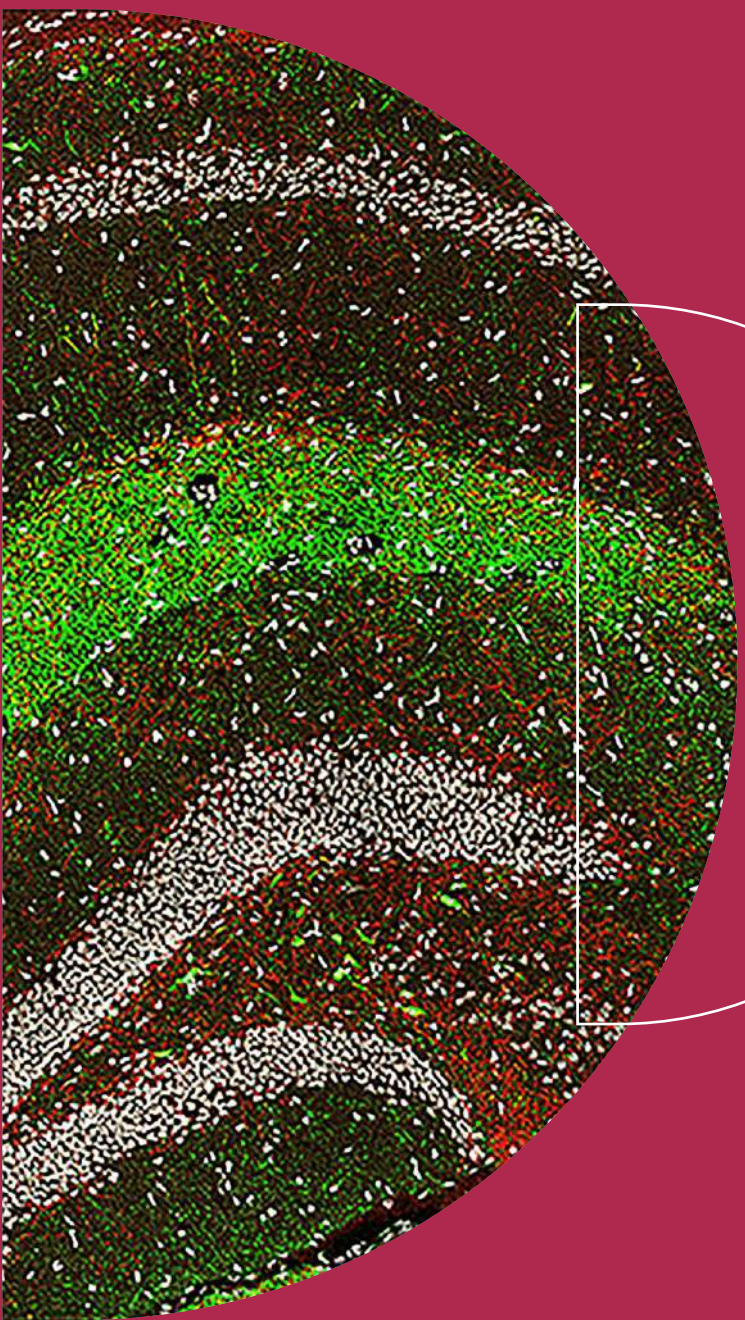
- Biosensors/Biointerfaces: understanding the fundamental physical mechanisms of acoustic biosensing in liquids
- Exploit this understanding in the detection of biomolecular structure and analysis of interactions at interfaces of biological or biotechnological interest. These include protein conformation, chain/chain (DNA, coiled-coils) interactions, protein adsorption and lipid bilayer structure
- Biopolymer hydrodynamics

A variety of techniques is employed such as: Acoustic Resonators (QCM-D), Spectroscopic Ellipsometry, SPR, ATR-InfraRed, Circular Dichroism, Viscometry, Adsorption Isotherms and Computer Modelling.

Current efforts focus on

- Analysing (via acoustic measurements) the attachment of the coiled-coil early endosomal antigen EEA1 onto early endosome-mimicking lipid membranes, the structure of this protein at such surfaces as well as the role of key lipids. Data regarding the attenuation of acoustic waves are exploited in order to extract information on the size and shape of the chain as these relate to hydrodynamic properties. Such structural information is valuable for better understanding membrane trafficking.
- Performing extensive analysis of the hydrodynamics of coiled-coil proteins via modelling; properties like the hydrodynamic radius and intrinsic viscosity of such linear molecules are described by scaling laws.

Web page https://www.gizeligroup.eu/achillestsortos



Neuroscience

Ioannis Charalampopoulos
Professor - Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers:
Konstantina Chanoumidou
Maria Anna Papadopoulou

PhD students:
Maria Kokkali
Despoina Charou
Alexandros Tsimpolis

Undergraduate thesis students:
Kaliopi Tamvaki
Elisavet Valera

NEUROPHARMACOLOGY / REGENERATIVE PHARMACOLOGY

Summary

Regenerative Pharmacology Lab, Medical School, UoC & IMBB-FORTH, Neurosciences Division

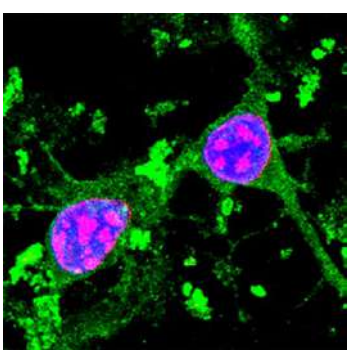
We are focusing our research interests on the investigation of the molecular mechanisms that growth factors and their receptors are using to regulate the regenerative capacity of nervous system. Such molecules, as Neurotrophins, control brain development and maintenance during adulthood and in aging, while they importantly participate in neuronal survival, differentiation and repair. Our studies are ranging from neurotrophin receptors structure-function experiments (Charalampopoulos et al., 2012, 2009) to development of novel ligands with specific effects on these receptors and their therapeutic potential on human and animal models of neurodegenerative diseases (Alzheimer's Disease and Spinal Cord Injury, Papadopoulou et al, 2023; Rogdakis et al., 2022, Charalampopoulos et al., 2004). The aim of our work is to decipher the multiple signalling effects of these receptors and thus to design and test novel analogs of their ligands with desired pharmacological properties (targeted signalling, small size, lipophilicity etc), targeting adult neurogenesis and neuroprotection in mouse models of neurodegenerative diseases, as well as in human induced Pluripotent Stem Cell-derived neural platforms, consisting of human neurons, oligodendrocytes and astrocytes co-cultured in 3D scaffolds (Kourgiantaki et al., 2020; Charou et al., under review).

Current aims

Neurotrophic factors consist key molecules for the development, survival and plasticity of the nervous system. Despite neurotrophins well-documented importance as neuroprotective and neurogenic molecules, the neurotrophin receptors exact expression and signaling properties are still largely unknown, especially for the pan-neurotrophin p75 receptor. We aim to reveal the role of neurotrophin receptors and their partners in neural stem cells during adult neurogenesis under neuropathological conditions, ranging from molecular to neural network level, emphasizing on Alzheimer's Disease. We develop 3D human platforms consisting of different neuronal cell types (neurons, astrocytes, oligodendrocytes) to resemble human neuropathologies and be used as platforms for drug screening.

Progress in 2022-2023

With the support of the European Innovation Council (EIC), the HORIZON2020-PATHFINDER grants, the Hellenic Foundation of Research and Innovation, Bodosakio Foundation, Institute of Pharmaceutical Research and Technology (IFET) and the General Secretary of Research & Innovation, we have developed a strong translational outcome of our research, based on important findings from basic research projects. Using animal models of Alzheimer's Disease, we have developed and characterize novel neurotrophin mimetics that selectively bind and activate specific neurotrophin receptors, revealing their role on adult neurogenesis and oligodendrogenesis in Alzheimer's Disease. Additionally, we have obtained human induced Pluripotent Stem Cell (hiPSC) lines from healthy donors and Alzheimer Disease patients, which we differentiate towards neuronal stem cells or mature neurons and glial cells, aiming to study human neurogenesis and to develop novel neurogenic compounds. Recently, upon finding from the HORIZON-European Innovation Council-PATHFINDER01-2022, we are coordinating an international program for the development of soft nanorobotic systems targeting drug delivery in the brain of human patients with Alzheimer's Disease (title: "SoftReach: Minimally Invasive Soft-Robot-Assisted Deep-Brain Localized Therapeutics Delivery for Neurological Disorders.", https://softreach.eu/index.php).



Confocal microscopy image of in vitro cultured proliferative oligodendrocyte progenitor cells (OPCs) under neurodegenerative conditions induced by the presence of toxic Amyloid-beta 1-42. The OPCs were immunostained for cell-specific PDGFRa marker (in green) and for Ki67 marker (in red) indicating proliferation. Hoechst dye (in blue) was used to stain nuclei of the total number of cells.
[Cover image for GLIA journal, Volume 72, Issue 4 (https://onlinelibrary.wiley.com/doi/abs/10.1002/glia.24399)]

Other activities

- Prof. Charalampopoulos is the Director of the Graduate Program in Neurosciences and representative of the Medical School in the University Committee for Graduate Programs.
- Co-founder of the ReNeuroCell Therapeutics, spin off company of FORTH and UoC.
- Our lab is participating in the IMBB-Mentoring Program.
- Our lab organized and participated in many events (e.g., Brain Week) for providing educational and professional information in high-school students, welcoming them at the lab for live exhibition of experimental protocols and discussion for the present and future of the biomedical sciences.

Web page: http://regenera-pharm.med.uoc.gr

Publications

Papadopoulou MA, et al. (2023) Neurotrophin Analog ENT-A044 Activates the p75 Neurotrophin Receptor, Regulating Neuronal Survival in a Cell Context-Dependent Manner. **Int J Mol Sci.** 24(14):11683

Kokkali M, et al. (2022) Biphasic Response of Astrocytic Brain-Derived Neurotrophic Factor Expression following Corticosterone Stimulation. **Biomolecules** 18;12(9):1322

Rogdakis T, et al. (2022) Development and Biological Characterization of a Novel Selective TrkA Agonist with Neuroprotective Properties against Amyloid Toxicity. **Biomedicines** 10(3):614

Emmanouil Froudarakis
Assistant Researcher (C)

GROUP MEMBERS

Principal Staff Scientist:
Athanasia Papoutsi
Postdoctoral fellows:
Maria Diamantaki
Constantina Georgelou
Research Assistant:
Alexandros Evangelou
PhD students:
Stamatis Aliprantis
Christos Paschalidis
MSc students:
Asimenia Goniotaki
Anastasios Gratsakis
Zeinab Ahmadi
Undergraduate thesis students:
Zoe Dogani
Elianna Petsalaki
Lab manager:
Agapi Ntretaki

SYSTEMS NEUROSCIENCE

Summary

Our lab investigates how cortical circuits across different brain areas interact to form multimodal object representations that can guide behavior. Natural scenes contain a large number of objects, and our brain is capable of using information from different sensory modalities to extract their identities with ease. Yet, despite extensive research in the last few decades, we are still far from having a complete understanding of how the brain creates untangled (transformation-invariant) object representations. If we understood how brains achieve this extraordinary ability at the algorithmic level, this would represent a significant advance in our understanding of cortical computation. To address this question, we combine advanced imaging techniques for recording neural activity with high-throughput behavioral training and computational modeling to study how the activity of large neuronal populations across different cortical regions enables behaving animals to identify and isolate objects in different contexts.

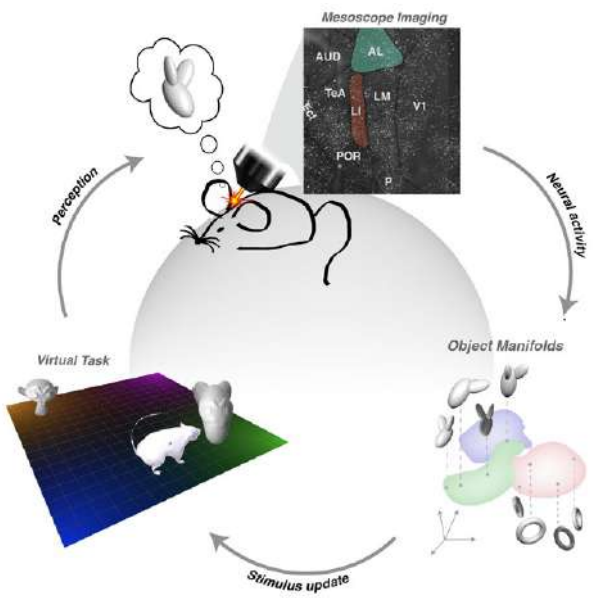
Current aims

The group's research focuses on:

i) How neural representations of objects evolve across the cortical hierarchy and how circuits in these areas interact in order to optimize the computations necessary for different behaviors.
ii) How these representations are modified during learning of new objects.
iii) Using object recognition in mice as a model to study cortical dysfunction.

Progress in 2022-2023

In order to address these questions, we have developed a software solution "EthoPy" that allows for an automatic, high-throughput and low-cost behavioral training system in which animals are trained to complex behavioral tasks in their home cage. In addition to these unique setups, we are developing an open-field setup that we can manipulate stimuli and other task parameters based on real-time tracking of the behavior of the animals (currently being funded by the ELIDEK), as well as a virtual environment in which head-immobilized animals can navigate based on the information from multiple sensory inputs (currently being funded by the ERC). These unique behavioral techniques will allow us to study cortical function with advanced recording techniques while animals are behaving. To study the role of higher visual areas for invariant object representation, we employ novel closed loop approaches including large-scale electrophysiological recordings from multiple visual cortical areas and deep learning modeling to generate a digital twin of the mouse visual cortex. The digital twin model allows for a detailed characterization of the optimal stimuli of the visual areas and offers a powerful tool for investigating feature selectivity across areas. Additional investigations are ongoing to uncover neural invariances across the visual hierarchy and how these are affected by the low-level properties we have characterized which will allow us to dissect the role of hierarchical processing in complex cortical computations such as invariant object recognition.



Other activities

- MSCA Individual Fellowship (Maria Diamantaki)
- ELIDEK grant (Research Projects to Support Faculty Members & Researchers)
- ERC Starting grant
- ELIDEK grant (Basic Research Financing Action (Horizontal support of all Sciences)
- Selected as FENS-Kavli Scholar
- Elected for General Secretary of the Hellenic Society for Neuroscience

Publications

Franke K, et al. (2022) State-dependent pupil dilation rapidly shifts visual feature selectivity. **Nature** 610:128–134

Liu Z, et al. (2022) Sustained deep-tissue voltage recording using a fast indicator evolved for two-photon microscopy. **Cell** 185(18):3408-3425. e29

Turner NL, et al. (2022a) Reconstruction of neocortex: Organelles, compartments, cells, circuits, and activity. **Cell** 185:1082-1100.e24

Achilleas Gravanis
Professor - Collaborating Faculty Member

GROUP MEMBERS

PhD students:
Konstantia Kodella
Konstantina Georgelou
George Stamatiadis
Antonio Varone
Ioanna Zota

NEUROPHARMACOLOGY

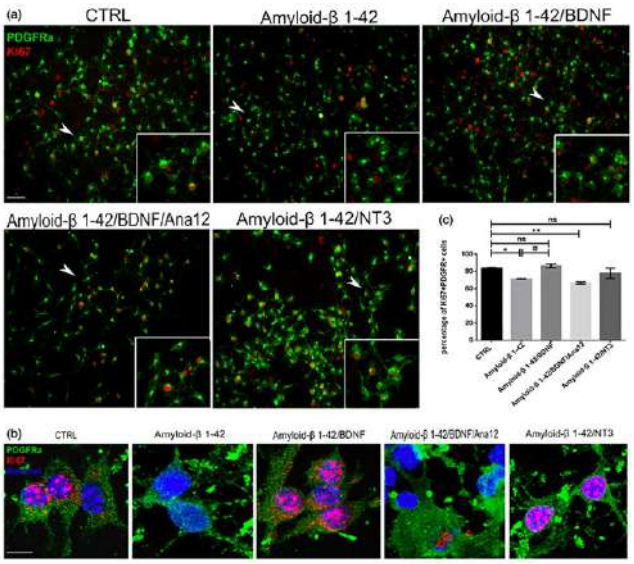
Summary

Our research group is developing synthetic compounds, agonists of neurotrophin receptors, with neuroprotective and neurogenic properties and potential applications in therapeutics of neurodegenerative diseases and brain ageing. Additionally, our group is focusing on organ-on-a-chip technologies and 3D microscaffold bioengineering, hosting neural stem cells to develop neuroimplants for spinal cord and brain injury and neurobiosensors for drug screening.

Current aims-Progress 2022-2022

Neural stem cell (NSC) grafts have demonstrated significant effects in animal models of spinal cord injury (SCI), yet their clinical translation remains challenging. We demonstrated that neuroimplants based on porous collagen-based scaffolds (PCSs), similar to biomaterials utilized clinically in induced regeneration, can deliver and protect embryonic NSCs at SCI sites, leading to significant improvement in locomotion recovery. Our neuroimplant induce regeneration in SCI lesions including enhancing NSC neuronal differentiation and functional integration in vivo, enabling robust axonal elongation, and reducing astrogliosis. Our findings suggest that the efficacy and translational potential of emerging NSC-based SCI therapies could be enhanced by delivering NSC via scaffolds derived from well-characterized clinically proven PCS. Our synthetic NGF mimetics showed efficacy in diminishing astrogliosis and increasing density of neurons in our neuroimplant, enhancing its efficacy.

We studied the importance of demyelination and its reversal by neurotrophin BDNF in the 5xFAD transgenic humanized model of Alzheimer disease (Zota et al Glia 2023). Recently, our group synthesized small molecules, mimetics of BDNF, activators of its receptor TrkB (new patent pending). Our innovative idea for Alzheimer's therapeutics is to combine NGF synthetic mimetics, activators of its receptor TrkA (Microneureotrophins, proprietary of our spinoff BioNature with the new synthetic BDNF mimetics to achieve stronger multimodal actions against neural death, neuroinflamnation and demyelination in AD, while boosting neural stem cells and de novo neurogenesis of fresh normal neurons, supplementing the suffering and lost ones.



In Alzheimer disease, besides neuronal cell death and neuro-inflammation, myelin formation and oligodendrocyte malfunction contribute significantly to loss of brain function and decreased cognitive abilities. Amyloid-β inhibits oligodendrocyte precursor cells (OPC) proliferation in vitro and in vivo in the humanized 5xFAD transgenic mice, an animal model of the disease. Neurotrophin BDNF reverses effectively the deleterious effects of amyloid-β in primary OPC cultures derived from P2 WT mice, exposed to amyloid-β (Zota et al, Glia 2023). We are testing now our synthetic BDNF mimetics, activators of TrkB receptor in in vitro and in vivo models of Alzheimer disease.

Other activities

- Efforts to translate our neuroimplant in patients with spinal cord injury were continued with Spaulding Rehabilitation Hospital (Harvard MS) in collaboration with Orgenesis SA (NY) which commits 4 million USD in the project and our new spinoff ReNeuroCell Therapeutics
- Our spinoff BioNature EA Ltd (www.bionature.net) finalizes discussions for licensing our compound BNN27 for its clinical evaluation in Diabetic Retinopathy
- Dr Gravanis was appointed Vice-Chair of the Board of Directors of the new Athens LifeTech Park (www.athenslifetechpark.com)

Web page http://gravanis.med.uoc.gr

Publications

Georgelou K, et al. (2023) Microneurotrophin BNN27 Reduces Astrogliosis and Increases Density of Neurons and Implanted Neural Stem Cell-Derived Cells after Spinal Cord Injury. **Biomedicines** 11:1170

Pediaditakis I, et al. (2022) A microengineered Brain-Chip to model neuroinflammation in humans. **iScience** 25:104813

Varone A, et al. (2021) A novel organ-chip system emulates three-dimensional architecture of the human epithelia and the mechanical forces acting on it. **Biomaterials** 275:120957

Domna Karagogeos

Professor - Collaborating Faculty Member

GROUP MEMBERS

Senior Staff scientist:
Kostas Theodorakis

Postdoctoral Researchers:
Theodora Velona
Ilias Kalafatakis
Vicky Stavroulaki
Dimitris Spyridakos

PhD students:
Zouzana Kounoupa
Niki Ktena
Stefanos Kaplanis
Sofia Petsaggouraki

MSc students:
Ariadni Papadaki
Lilian Peppa
Alexandros Georgilis
Andriana Lygeraki
Despoina Kaffe
Iason Sifakis

Undergraduate thesis students:
Fevronia Papagianni
Evrim Kagia
Theofania Tsitsopoulou
Sissy Thomoglou
Athanasia Voulgari
Manos Karatheodorou
Anastasia Klironomou

NEURAL DEVELOPMENT

Summary

Myelin is the multilamellar, lipid-rich membrane that wraps the majority of vertebrate axons and ensures the rapid action potential propagation. Myelinated fibers are segregated into functionally distinct domains, which are particularly vulnerable in demyelinating pathologies such as multiple sclerosis. We focus on a) testing molecules that may influence demyelination/remyelination b) investigating the role of autophagy in CNS myelin homeostasis.

Neurodevelopmental pathologies originate often as a result of perturbed balance of excitation and inhibition due to defects in interneurons. We have generated and are analyzing two genetic models of decreased inhibition and are investigating the myelinating properties of interneurons in transgenic lines.

Current aims

i) **CNS myelin homeostasis and disruption.** We are investigating the role of autophagy as an essential mechanism of myelin homeostasis. By ablating or inducing autophagy by selected compounds we are analyzing the myelin status using *in vitro, ex vivo* and *in vivo* models.

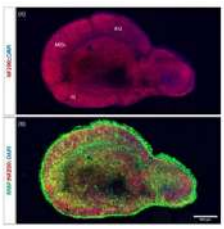
ii) **Molecular and functional analysis of models of decreased inhibition in the cerebral cortex.** We aim to understand the role of Rac1 and 3 in interneuron maturation. Currently we focus on the characterization of their defects via novel, state-of-the-art approaches.

iii) **Myelination properties of hippocampal interneurons**. The majority of myelin in the hippocampus is found on axons of inhibitory neurons. We aim to understand the function of myelin in these cells using a Cre-loxP system that will specifically ablate a molecule expressed by their axons.

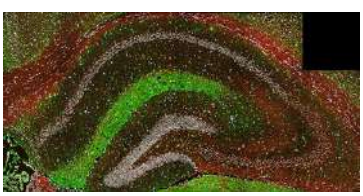
Progress in 2022-2023

a) We showed that the maintenance of CNS myelin homeostasis requires a fully functional autophagic machinery. Using *in vitro* and *in vivo* approaches, we provided evidence that: autophagy is necessary for oligodendrocyte (OL) maturation, myelin proteins are found in autophagosomes in OLs while autophagic ablation in OLs leads to myelin defects, increased axonal degeneration and behavioral deficits (Ktena et al, 2022). Autophagic induction by caloric restriction mimetics enhanced both myelination and remyelination, through a direct effect in astrocytes and microglia that promotes a less inflammatory environment (Kaplanis et al, 2023). We participated in collaborative work on the use of biobased and biocompatible nanomolecules for drug encapsulation, drug delivery and treatment. The main goal of this project was to use novel nanoparticles to deliver known agents that could improve remyelination *in vivo*.

b) Upon Rac1 and Rac3 ablation, centrosome, Golgi complex and lysosome positioning is significantly perturbed, thus affecting both migration and axon growth, while the two-pore channel 2 (TPC2) voltage-gated ion channel that mediates Ca^{2+} release, contributes to this phenotype of decreased inhibition (Kounoupa et al, 2023).



Confocal image of prefrontal area of organotypic mouse brain slices from postnatal day 4 mice (A) neurofilament (red) and nuclear staining (blue). The three cortical layers (Ald: Agranular insular area, Mos: secondary motor area and PL1: prelimbic area) can be distinguished. (B) Axons (red) and myelin (green) in the prefrontal area of P4 mice ex vivo. Scale bar: 500 μm.



Coronal section of an adult mouse hippocampus depicting one of the two hemispheres stained for Myelin Basic Protein (MBP) in red, Somatostatin (Sst+) interneurons in green, and nuclear staining in white.

Other activities

- D. Karagogeos has been elected to the IBRO (International Brain Research Organization) Pan-Europe Regional Committee (PERC) and is a member of the FENS (Fed. of European Neuroscience Societies)-Committee of Higher Education and Training which supports continued higher education and training in Neuroscience.
- Member of the Recruitment and Training Working Group of EU Life and a member of the IMBB Mentoring Committee.
- Member of the executive committee of HELANA (Hellenic Academy of Neuroimmunology)
- Co-organized the Symposium on “Humanized cell-derived models for better understanding CNS development, myelination and brain pathologies” in the 11th IBRO World Congress of Neuroscience, Granada, Spain and the FENS-SFN webinar on Myelin Plasticity (2023)
- Teaching duties: Biology to medical students and Neurobiology in three graduate programs of the University of Crete.
- Awarded EREYNV KAINOTOMV (NanoMythic), HFRI (INTER_RAC) and SYNERGY (RENEW) grants; S. Kaplanis received the S. Altman Fellowship; N. Ktena received the IKY Graduate Fellowship

Web page http://www.imbb.forth.gr/en/research-en/neurosciences/item/70-domna-karagogeos

Publications

Kounoupa Z, et al. (2023) Rac1 and Rac3 GTPases and TPC2 are required for axonal outgrowth and migration of cortical interneurons. **J Cell Sci.** (2023) 136(6): jcs260373 doi: 10.1242/jcs.260373

Kalemaki K, et al. (2022) The developmental changes in intrinsic and synaptic properties of prefrontal neurons enhance local network activity from the second to the third postnatal weeks in mice. **Cereb. Cortex** 32(17):3633-3650 doi: 10.1093/cercor/bhab438

Ktena N, et al. (2022) Autophagic degradation of CNS myelin maintains axon integrity. **Cell Stress** 6(12):93-107 doi: 10.15698/cst2022.12.274

Panayiota Poirazi
Research Director (A)

GROUP MEMBERS

Postdoctoral researchers:
George Kastellakis
Spyridon Chavlis
Anthi Apostolopoulou

PhD students:
Michalis Pagkalos
Kostas Petousakis
Ioanna Pandi
Maria Protopapa
Roman Makarov
Simone Tasciotti

MSc students:
Anna Tsiamanta,
Christos Karageorgiou Kaneen
Ioannis-Rafail Tzonevrakis
Elisavet Kapetanou

Undergraduate thesis students:
Erinni Mantouvalou
Sotiris Dimitriou

Lab manager:
Marsa Velissariou

SYSTEMS NEUROSCIENCE

Summary

Dendrites are thin processes that emerge from the cell body of neurons. They receive over 90% of the synaptic inputs to neurons, integrate them in non-linear ways thus expanding the processing power of neurons and their properties are altered in neurodegenerative conditions, making them targets for new treatments. We are interested in understanding how dendrites contribute to brain functions in health and disease and whether dendritic features can help advance artificial intelligence. We tackle this problem using a multidisciplinary approach that includes computational modeling, experiments in mice and machine learning methods.

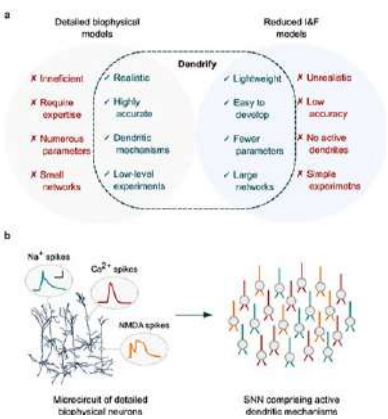
Current aims

We currently investigate how dendrites of different cell types contribute to neuronal and network computations that determine behavior. We build computational models of various complexity levels and combine them with experiments in rodents to study dendritic contributions to functions like learning, memory and behavioral flexibility. In addition, we adopt key dendritic features in machine learning algorithms with the goal to advance their efficiency and computing capabilities. Finally, we have been developing a smart, drug discovery platform, whereby an Alzheimer's circuit model drives cultured neurons on nanowire arrays in a closed-loop manner. The model can drive specific disease states in the cultured neurons, enabling users to evaluate the efficacy of drugs in restoring these pathological conditions.

Progress in 2022-2023

In the past two years, our lab has made important contributions to the fields of neuroscience and bio-inspired machine learning:

i) We introduced the Dendrify framework for building simplified yet realistic spiking neuron models with dendrites. The new Dendrify tool is widely adopted by the Neuroscience community (Pagkalos et al, *Nat. Commun.* 2023, https://dendrify.readthedocs.io/en/latest/)
ii) We showed how apical and basal dendrites of L2/3 pyramidal neurons in the visual cortex interact to shape the selectivity of these neurons (Petousakis et al, eLife, 2023).
iii) We published several review/opinion papers that discuss how dendrites contribute to advanced brain functions and how they can serve as a source of inspiration for optimizing machine learning algorithms (Makarov et al, *Current Opinion in Neurobiol*, 2023; Petousakis et al, Acharyaa et al, Neuroscience 2021, Chavlis and Poirazi, Current Opinion in Neurobiol, 2021)
iv) We adopted dendritic properties such as synaptic turnover (Malakasis et al, 2023), dendritic receptive fields (Pinitas et al, 2022) and structure (Chavlis and Poirazi, 2023), axonal delays (Iacob et al, 2023) and showed their potential to advance machine learning and artificial intelligence (Troullinou et al, 2023).
v) Together with our collaborator Alcino Silva at UCLA, we combined models and experiments to explain how dendritic excitability underlies memory linking (Chowdhury, et al, 2022)
vi) Last but not least, the first results from our experimental branch of the lab regarding the role of spine dynamics in flexible behavior were presented in numerous international conferences (FENS Regional meeting 2023, FENS Brain Conference 2023, HSfN 2023).



a. Dendrify stemmed from our efforts to bridge the gap between detailed biophysical models and reduced I&F models. The result is a modeling framework for developing simplified compartmental models that balance efficiency and biological accuracy by capturing the most important characteristics of both worlds. b. Dendrify facilitates the development of SNNs comprising reduced compartmental neurons (ball and sticks) and known dendritic phenomena, such as various types of local spikes (Color code; teal: Na+ spikes, red: Ca2+ spikes, orange: NMDA spikes. Scale bar: 20 mV/10 ms).

Other activities

- Dr. Poirazi currently serves as the Secretary General Elect of the Federation for European Neuroscience Societies (FENS).
- Dr. Poirazi was a Plenary Speaker at the FENS Forum 2022, the largest Neuroscience meeting in Europe and the Hellenic Society for Neuroscience meeting in 2023.
- In 2022, the 4th edition of the EMBO Workshop on Dendrites was organized in Heraklion, Crete by Dr. Poirazi and Profs. M. Larkum, M. Hausser and K. Harris.
- Several people from our lab received competitive fellowships/awards in 2022 and 2023: Postdoctoral fellow Spiros Chavlis won the best oral presentation award at the Symposium on the mathematics of Neuroscience in 2022. Postdoctoral fellow Anthi Apostolopoulou received a Marie Curie Fellowship in 2022. PhD student Ioanna Pandi received travel awards to present her work at the FENS 2023 Regional meeting, the HSfN 2023 meeting and the 2023 Brain Conference; PhD student Roman Makarov received a HSfN 2023 travel award.

Web page www.dendrites.gr

Publications

Petousakis KE, et al. (2023) Modeling apical and basal tree contribution to orientation selectivity in a mouse primary visual cortex layer 2/3 pyramidal cell. **Elife** 12: e91627 doi: 10.7554/eLife.91627

Bilash OM, et al. (2023) Chavlis S, Johnson CD, Poirazi P, Basu J. Lateral entorhinal cortex inputs modulate hippocampal dendritic excitability by recruiting a local disinhibitory microcircuit. **Cell Reports** 42(1):111962 doi: 10.1016/j.celrep.2022.111962

Pagkalos M, et al. (2023) Introducing the Dendrify framework for incorporating dendrites to spiking neural networks. **Nature Communications** 14(1):131 doi: 10.1038/s41467-022-35747-8.

Kyriaki Sidiropoulou
Associate Professor and Collaborating Researcher

GROUP MEMBERS

Post-doctoral researcher:
Angeliki Velli

Ph.D. students:
Lida Vagiaki
Konstantinos Diskos
Maria Plataki

MSc students:
Chrysoula Iordanidou
Zoe Drakaki
Olga Lyraki

Undergraduate thesis students:
Ifigeneia Ioannidi
Stavriana Panayiotou
Samuele Torrini
Maria Nazou
Iliana Gloula
Niki Tyraki
Dimitris Antoniadis
Marina Paschalidi

NEUROPHYSIOLOGY & BEHAVIOR

Summary

Research in the "Neurophysiology and Behavior" laboratory (www.sidiropouloulab.com) focuses on three main topics: 1) investigating the cellular mechanisms involved in the function of the prefrontal cortex and the hippocampus, 2) understanding the developmental neurobiological alterations that occur in neurodevelopmental mouse models of schizophrenia and 3) delineating the mechanisms of action of novel antiepileptic drugs.

Current aims

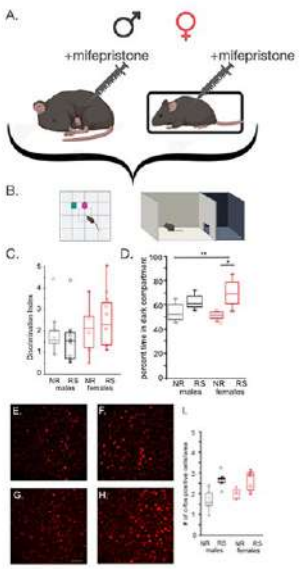
Our current aims include:

i) to delineate the developmental trajectories of neurophysiological mechanisms in the prefrontal cortex and the hippocampus, in wild-type animals and an animal model of schizophrenia
ii) dissect the mechanism underlying sex differences in the prefrontal cortical function following acute stress exposure.

Progress in 2022-2023

With regards to our first research aim, we have published a study in which we delineate the developmental trajectory of intrinsic electrophysiological properties as well as synaptic mechanisms of pyramidal neurons and GABAergic interneurons (Kalemaki et al., 2022). Since then, we are conducting experiments in adolescent and adult mice, as well as in all age groups of the MAM mouse model of schizophrenia. We have already identified specific neurophysiological adaptations in adolescent MAM mice and are planning interventional experiments to determine whether schizophrenia symptoms can be rescued following a reset of the altered neurophysiological mechanisms. These data have been presented in the European Brain and Behavior Society meeting in August 2023.

With regards to our second research aim, we have published a study in which we show that acute restraint stress impairs performance in recency memory (tested with temporal order object recognition), long-term potentiation and neuronal activation in male mice, but not female mice. Blocking the activity of glucocorticoid receptors restores the stress-induced impairments (Velli et al., 2022). Follow-up research identified that female mice reduce their inhibitory function in the prefrontal cortex following glucocorticoid receptors, a mechanism that could subserve resilience to the stress-induced effects in female mice.



Mifepristone reverses the impaired cognitive function and reduced neuronal activation induced by the restraint stress.
A. Experimental design. Male and female mice received i.p. injections of mifepristone (a glucocorticoid receptor antagonist) before subjected to 2hours of restraint stress (right) or not (left). B. Following stress exposure, mice were subjected to the light-dark test to test for anxiety and the temporal order object recognition (TOR) task to test cognitive function. C. There is no signficant difference in the discrimination index in the TOR task in either males and females, when in the absence of mifepristone males exhibit reduced discrimination index. D. Female mice, even in the presence of mifepristone, spent increased time in the dark compartment, therefore, antagonism of the glucocorticoid receptor does not restore anxiety levels. E-I: The levels of c-fos expression are increased following restraint stress both in males and females, while male mice did not exhibit increased c-fos expression in the absence of glucocorticoid receptor antagonism

Other activities

Dr. Sidiropoulou participated as a speaker in the European Brain and Behavior Society meeting in August 2023, which took place in Amsterdam. She organized the symposium titled "Cellular and network properties of the prefrontal cortex across development: effect on behaviour" in which she gave a talk titled "Development of cellular of the prefrontal cortex: from neurons to networks". Furthermore, she was an invited speaker in the Hellenic Society for Neuroscience meeting which took place in November 2023 in Athens. During 2022, she served as an ordinary member in the General Council of EBBS. The Neurophysiology and Behavior Laboratory participated in outreach activities in 2019 and 2020, including the Brain Awareness Week and the Marie-Curie Researcher's Night.

Web page www.sidiropouloulab.com/home

Publications

Thomaidi M, (2022) Local anaesthetics via multicomponent reactions. **ChemMedChem** 17(15): e202200246. doi: 10.1002/cmdc.202200246

Velli A, (2022) Sexual dimorphic effects of restraint stress on prefrontal cortical function are mediated by glucocorticoid receptor activation. **European Journal of Neuroscience** 55(9-10):2754-2765 doi: 10.1111/ejn.15203

K. Kalemaki K, (2022) The developmental changes in intrinsic and synaptic properties of prefrontal neurons enhance local network activity from the second to the third postnatal week in mice. **Cerebral Cortex** 32(17):3633-3650 doi: 10.1093/cercor/bhab438

Konstantinos Theodorakis
Senior Staff Scientist-Karagogeos Lab

NEURAL DEVELOPMENT

My scientific interests focus on the biology of the nervous system and especially on neuronal development and axoglial interactions during myelination.I have participated in several research projects related to myelination and demyelinating diseases.Since 2018 we have initiated two research projects concerning the use of biobased and biocompatible nanomolecules for drug encapsulation, drug delivery and treatment. The main goal of the first project is the use of novel nanoparticles to deliver known agents that could improve remyelination in vivo. In particular, we are currently working on "NANOMYTHiC" - (T2EDK-00501), a program where we employ innovative nanocarriersfor the targeted and prolonged treatment of demyelinating diseases of the central nervous system.The second project focused on the use of multifunctional patches from natural and synthetic polymers for the treatment of wounds, following the stages of hemostasis,tissue regeneration and finally wound healing. During my scientific career I have worked with multiple experimental models, such as chick embryos, mice, and various mammalian neuronal and other cell lines.My technical expertise includes several molecular and biochemical techniques, like gene cloning, PCR, mouse genetics, protein and mRNA expression analysis (immunohistochemistry/immunofluorescence and in situ hybridization respectively), real time PCR, cell culture, tissue cultures, brain slice electroporation, FACS, in utero electroporation etc.

Web page https://www.imbb.forth.gr/imbb-people/en/members-karagogeos/item/1803-kostas-theodorakis

Athanasia Papoutsi
Principal Staff Scientist-Froudarakis Lab

COMPUTATIONAL NEUROSCIENCE

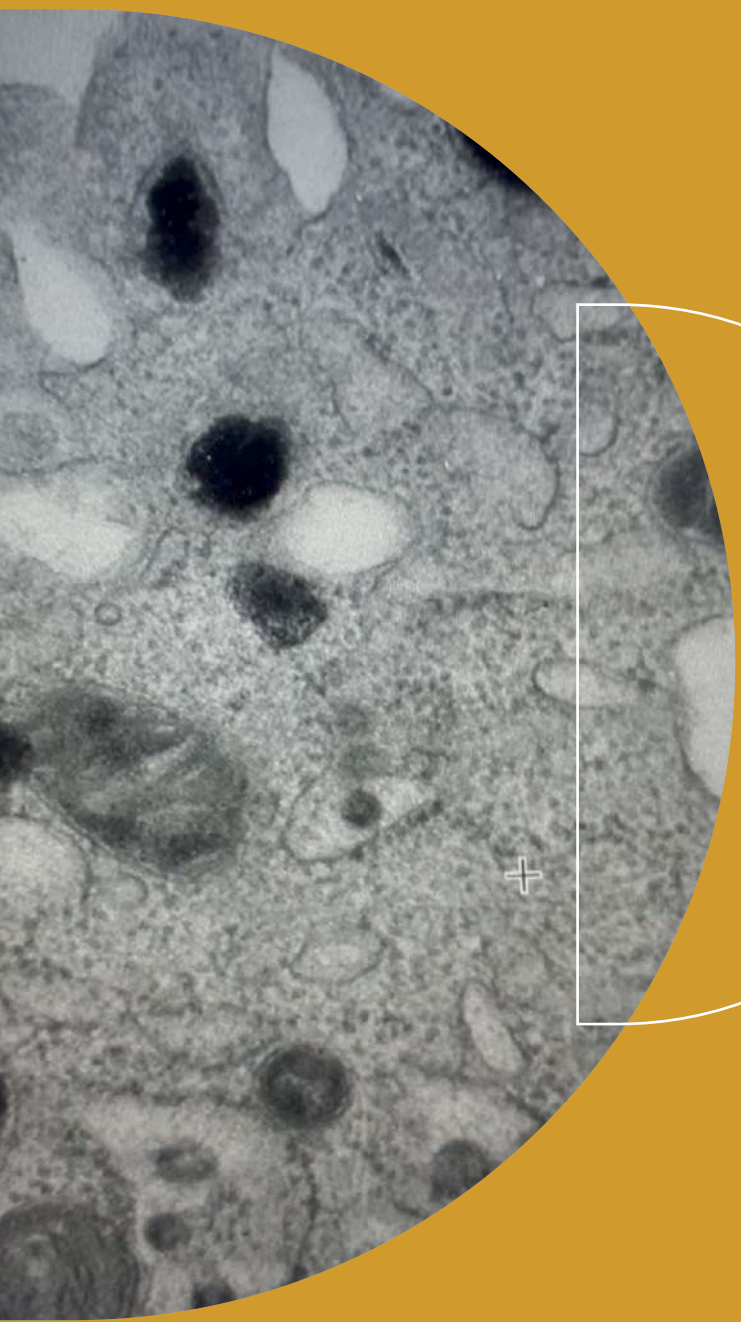
From the processing of environmental sensory cues to more elaborate cognitive functions, such as decision making, the mammalian brain has evolved to efficiently resolve the task at hand. Alongside, the basic building blocks of the neocortex, the pyramidal neurons, have adapted to perform diverse computational tasks, greatly enriching the achieved functions at the systems level. We investigate the properties of these computations, how they are regulated at the circuit level and how they are linked to specific behaviours, such as flexible decision making. We are also interested in how this machinery is dysregulated in pathological conditions. To achieve these goals, we combine optogenetic stimulation, two-photon imaging, genetic and behavioral approaches with theoretical modelling in order to perform physiological studies of pyramidal neurons *in vivo* and *in silico*. With the support of the FORTH Synergy grant (2022-2024), we have developed a novel set-shifting task that requires animals to dynamically modify their behavioral strategy by responding to stimuli that were previously irrelevant. Using this task, we are currently investigating the functional interaction between prefrontal cortex (PFC) and the mediodorsal thalamus (MD) and how this interaction supports the 'aha moment' during behavioral transitions.

In 2022-2023 Dr. Papoutsi was invited speaker in The CapoCaccia Workshops toward Neuromorphic Intelligence, Alghero, Italy (2023) and participated in the organization of:

- the Computational Neuroscience Society meeting in Melbourne, Australia (2022) and Leipzig, Germany (2023),
- a COSYNE Workshop in Montreal, Canada (2023),
- the 15th Advanced Scientific Programming in Python Summer School in Heraklion, Greece (2023)
- a FENS Symposium in Paris, France (2022).

Her recent publications are: Nordentoft MS, Papoutsi A, Takahashi N, Heltberg MS, Jensen MH, Rasmussen RN (2023) Local changes in potassium ions modulate dendritic integration. bioRxiv:2023.05.06.539205., b) Ishikawa T, Ishikawa AW, Papoutsi A, Tanimura A, Yonehara K (2023) Editorial: Subcellular computations and information processing. Front Synaptic Neurosci 15:9. and c) Petousakis K-E, Park J, Papoutsi A, Smirnakis S, Poirazi P (2023) Modeling apical and basal tree contribution to orientation selectivity in a mouse primary visual cortex layer 2/3 pyramidal cell. Elife 12.

Web page https://www.imbb.forth.gr/papoutsi



Immunity

George Bertsias

Assistant Professor - Collaborating Faculty Member

GROUP MEMBERS

Senior researcher:
Maria Semitekolou

Post-doctoral researcher:
Chrysoula Stathopoulou

PhD students:
Despoina Kosmara
Dimitra Nikoleri
Sofia Papanicolaou

MSc student:
Konstantina Pambouka

SYSTEMIC AUTOIMMUNITY & INFLAMMATION

Summary

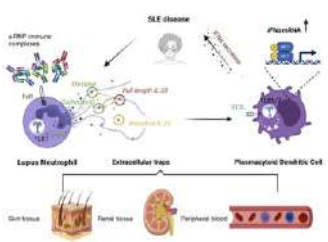
Laboratory of Rheumatology, Autoimmunity and Inflammation - Systemic Autoimmunity and Gene Regulation Unit. Our focus is on the regulation of innate and adaptive immunity, focusing on molecular, epigenetic and metabolic pathways implicated in autoimmunity. We use human and murine Systemic Lupus Erythematosus (SLE) as a disease-model, and apply targeted assays and high-throughput technologies in tissues in order to decipher the genomic basis of specific phenotypes (such as gender bias) and outcomes (response or failure to treatments, fibrosis) of the disease.

Current aims

- Driven by our results from a blood RNA-sequencing study in patients with lupus, we explore the role of chromatin regulators such as the cohesin complex in the genomic perturbations and monocytes activation in males and females with SLE. Our results indicate that SMC1A/cohesin is recruited at the active enhancers of genes implicated in inflammatory response and this might serve as an explanation for the robust immune responses in females, thus predisposing them autoimmunity.
- We also explore how interferon-alpha, a hallmark cytokine implicated in autoimmunity, can modulate intracellular processes and metabolic pathways involved in monocyte activation in the context of autoimmunity. By the use of biochemical, immunochemical, transcriptome and high-throughput technologies, we investigate the glycolytic and cholesterol biosynthesis pathways and identify regulators which might represent novel therapeutic targets for immune-related diseases.
- Motived by our previous research demonstrating that IFN-alpha enhances autophagy in monocytes, we also examine the role of autophagic machinery in facilitating the secretion of B-cell activating factor (BAFF), a cytokine that promotes B-cell activation and maturation in autoimmunity. We hypothesize that under the effect of IFN-alpha, BAFF is directed into autophagy vesicles and excreted via exosomes to interact with BAFF-receptor-expressing B-cells.
- Finally, we seek to understand the intra-renal cellular and molecular networks accounting for the development and progression of kidney disease in NZB/W lupus-prone mice, focusing on the pivotal role of cytokines such as interferon and IL-17.

Progress in 2022-2023

- We identified IL-33 as a novel alarmin that decorates extracellular chromatin traps (NETs) derived from SLE neutrophils. IL-33 NETs infiltrate various tissues in lupus and may potentiate the production of type I IFN by plasmacytoid dendritic cells. This effect is mediated by the IL-33 receptor, ST2L. This work was published in *JCI Insight*.
- We analysed the genome regulatory role of SMC1A/cohesin complex protein in the context of SLE autoimmunity. Our findings indicate that SMC1A may facilitate the transcriptional activation of numerous inflammatory genes/pathways involved in inflammation. The increased expression of SMC1A in women than men with SLE could represent a novel molecular mechanism predisposing to autoimmunity. These results have been presented in international meetings and a manuscript has been submitted.
- We found that SLE monocytes with high interferon gene signature have upregulated glycolytic and cholesterol synthesis pathways, which contribute to production of inflammatory cytokines (TNF, IL-1β) and expression of costimulatory receptors. Statin administration or targeting specific IFN-inducible genes implicated in cholesterol biosynthesis were able to ameliorate the inflammatory phenotype of monocytes. This work has been in international meetings and a manuscript is currently under preparation.
- In collaboration with the group of Christoforos Nikolaou (BSRC "Alexander Fleming") we explored the pattern of alternative splicing in the blood of patients with SLE compared to healthy individuals. Spliced isoforms of several immune-related genes/pathways were found to be deregulated according to disease activity level and to demonstrate sex-bias, thus proposing a role for this often-overlooked layer of transcriptome/molecular variation in autoimmunity.
- We established in the lab two mouse models of lupus, the NZB/W F1 spontaneous model and the pristane inducible model which are currently undergo phenotypic, immunologic and histological (kidney, skin, lungs) characterization in order to assist the ongoing and future projects in the lab.



Activated neutrophils in systemic lupus erythematosus externalize chromatin extracellular traps bearing protease-activated IL-33 that induces type I interferon production, contributing to disease perpetuation (obtain from *JCI Insight*. 2021; 6: e147671).

Other activities

- Through prospective evaluation of a cohort of pregnant SLE women, we found that achievement of low disease activity or remission is linked to better obstetric outcomes as compared to counterparts who do not achieve these treatment targets.
- We joined a European task force that proposed assays for the detection/quantification of type I interferon and the clinical interpretation of the results.
- Together with other colleagues, the PI led an international Task Force for the update of the EULAR (European Alliance of Associations for Rheumatology) recommendations for the management of SLE.

Web page: https://www.imbb.forth.gr/en/research-en/infections-immunity/item/4187-george-bertsias

Publications

Kosmara D, (2023) Extensive Alternative Splicing Patterns in Systemic Lupus Erythematosus Highlight Sexual Differences. **Cells** 12(23):2678

Emmanouilidou E, (2023) Progressive Multifocal Leukoencephalopathy in Systemic Lupus Erythematosus: A Consequence of Patient-Intrinsic or -Extrinsic Factors? **J Clin Med.** 12(21):6945

Garantziotis P, (2022) Molecular Taxonomy of Systemic Lupus Erythematosus Through Data-Driven Patient Stratification: Molecular Endotypes and Cluster-Tailored Drugs. **Front Immunol.** 13:860726

Georgios Chamilos

Professor - Collaborating Faculty Member

GROUP MEMBERS

Post-doctoral Researchers:
Irene Kyrmizi
Tonia Akoumianaki
Ioannis Morianos
Zoi Veneti

PhD Students:
Electra Nenedaki
Vasilis Nidris
Stavroula Baiba
Alexandra Vatikioti
Marina Gkountzinopoulou
Manthos Sertedakis

Research Assistant:
Aggeliki Vogiatzi

FUNGAL IMMUNOLOGY

Summary

Airborne filamentous fungi (molds), mainly Aspergillus and the Mucorales, are major causes of respiratory diseases in an expanding population of patients with complex immunometabolic defects. Invasive mold infections (IMI) are associated with substantial mortality and enormous economic impact. Understanding pathogenesis of IMI is an unmet need for design of better therapies. Focus of our research is to identify specialized host effector mechanisms employed by professional phagocytes during dynamic interactions with opportunistic molds, and fungal pathogenetic strategies that subvert physiological immune responses. Ultimate goal of our research is to develop (i) novel biomarkers of immune deactivation (immmunoparalysis) to stratify patients at high risk for IMI and (ii) host-directed therapies that enhance fungal clearance, prevent immunopathology, and improve disease outcome.

Current aims

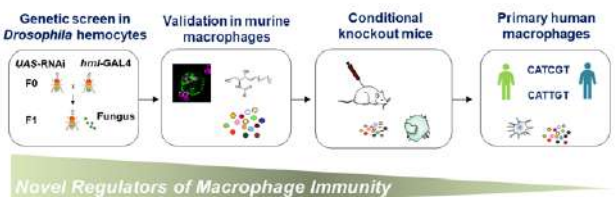
Studies from our group put forward a novel mechanism for the pathogenesis of IMI, according to which development of IMI requires two discrete mechanisms (a) phagosome maturation arrest (via inhibition of LC3-associated phagocytosis, LAP), which allows intracellular persistence of fungal conidia (spores), and (b) alteration in iron homeostasis, resulting in invasive fungal growth and lysis of the macrophage. According to this model iron regulation inside macrophages is the last and most critical line of host defense against molds. On the pathogen site, our pilot studies imply that fungal melanin profoundly alters macrophage metabolism and metal homeostasis. Collectively, these findings put forward the hypothesis that mold infection triggers novel regulatory schemes influencing iron metabolism in macrophages.
Aim of our research is to identify the key regulators involved in fungal infection-triggered iron metabolism reprogramming and elucidate its role in the pathogenesis of IMI. These studies will set the basis for future research that will address long-standing fundamental questions on macrophage iron biology, metabolism and inflammation.

Progress in 2022-2023. Completed Projects:

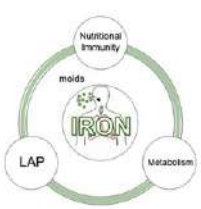
We identified a novel mechanism of immune deactivation in sepsis that links defective IL-6 signaling with LAP blockade. We also discovered that physiologically, IL-6/JAK2 signaling regulates microtubule organization and ERK trafficking to the phagosome for activation of LAP. This work delinates a novel mechanisms of sepsis immunosupression and provides a new molecular link between cytokine signaling, endosomal traficking and LAP-dependent phagosome respones. In collaboration with Agostinho Carvalho lab we have revealed the inhibition of calcium signaling by fungal melanin triggers an immunometabolic signaling axis towards glycolysis via activation of HIF-1α and phagosomal recruitment of mTOR, which is essential for antifungal host defense. In collaboration with Ashraf Ibrahim lab, we identified the important role of a novel ricin-like toxin produced by Mucorales molds in pathogenesis of invasive fungal disease and we identified host lipid effectors that target the expression of this toxin to block fungal pathogenicity *in vivo*.

Ongoing projects

- *Novel mechanisms of activation of LAP during Aspergillus infection*
- *Role of lipid metabolism on LAP-dependent and LAP-independent host defense mechanisms in macrophages*
- *Novel antifungal effector function of physiological host lipids*
- *Dissecting the role of iron in immunometabolism and antifungal immunity of macrophages*
- *Molecular mechanisms of immunosuppressive activity of corticosteroids in IMI*
- *Novel antifungal activity of neutrophils regulated by lipid signaling*



Experimental strategy to dissect the role of evolutionarily conserved mechanisms of antifungal host defense in phagocytes



Proposed model on the central role of iron in antifungal immunity. Apart from regulating nutritional immunity, iron controls macrophage immunometabolism, inflammation and phagosome responses (LAP).

Other activities

- Hosted undergraduate and rotation students for training.
- The lab coordinated a clinical protocol for salvage treatment of patients with severe COVID-19 with convalescent serum
- ELIDEK Postdoctoral award to John Morianos (2021)
- ELIDEK PhD student award to Stavroula Baiba (2021)
- The Sidney Altman Scholarship Program Award to Alexandra Vatikioti, 2023
- Award for the Best Poster Presentation in11th Advances against Aspergillosis and Mucormycosis Conference, to Irene Kyrmizi, 2023
- The lab is Coordinating a Multicenter National Pneumonia Study (Pro-sCAP) to dissect dissect pathogenesis and complications of severe community acquired pneumonia (CAP), including fungal superinfections

Web page https://cmmp.med.uoc.gr/index.php/intro-hdfp

Publications

Akoumianaki T, et al. (2021) Uncoupling of IL-6 signaling and LC3-associated phagocytosis drives immunoparalysis during sepsis. **Cell Host Microbe** 29(8):1277-1293.e6

Soliman SSM, et al. (2021) Mucoricin is a ricin-like toxin that is critical for the pathogenesis of mucormycosis. **Nat Microbiol**. 6(3):313-326 doi: 10.1038/s41564-020-00837-0

Gonçalves SM, et al. (2020) Phagosomal removal of fungal melanin reprograms macrophage metabolism to promote antifungal immunity. **Nat. Commun.** 11(1):2282

Prodromos Sidiropoulos
Professor - Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers:
Eirini Sevdali
Eirini Flouri

PhD students:
Panagiota Goutakoli
Elpida Neofotistou Themeli

REUMATOLOGY, AUTOIMMUNITY & INFLAMMATION

Summary

Inflammatory Arthritides

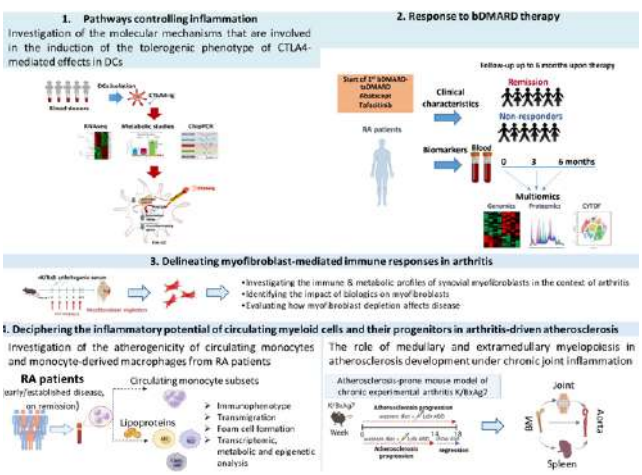
The *Laboratory of Rheumatology, Autoimmunity and Inflammation of the Medical School* together with the *Rheumatology Clinic (Clinical Research Unit) at the University Hospital of Heraklion*, represent an interdisciplinary group of physician scientists, bio-scientists, clinicians and nurses, which investigate inflammation in the context of *chronic autoimmune inflammatory diseases (CAID)*. The laboratory explores mechanisms contributing to dysregulated immune responses with the ultimate goal of developing *novel biomarkers and therapies*. We use animal models of rheumatoid arthritis as well as tissues obtained from humans (blood, bone marrow, skin, synovium) to investigate innate and adaptive immune responses under the premise that they share common effector pathways for tissue injury. Importantly, we explore the relative contribution of these pathways in human diseases by studying well characterized patient cohorts, seeking to identify *molecular biomarkers for diagnosis and predictors of response to therapies-outcome*. We aim to understand how novel therapies work and explore molecular or *genetic biomarkers that predict response or toxicity to therapy*.

Current aims

1. **Mechanisms contributing to dysregulated immune response in inflammatory arthritis (Rheumatoid Arthritis-RA).**
   A. Among the cellular mechanisms controlling immune responses are tolerogenic dendritic cells (tolDCs). We currently investigating molecular pathways with an emphasis in cellular metabolism, operable in tolDCs and how they may be affected by biologic therapies.
   B. Fibroblasts are important contributors to the articular inflammation in RA. We aim to explore their cellular interaction with synovial immune cells and investigate intracellular molecular and metabolic function in the context of RA. Transgenic mouse models for fibroblast's depletion-isolation are being applied.
2. **Atherosclerosis development in the context of chronic inflammatory diseases:** The molecular and cellular mechanisms contributing to CAID-associated atherosclerosis are not well characterized. Applying various models of arthritis (DBA1, STIA) and a model combining inflammatory arthritis with atherosclerosis (K/BxN) we aim to understand the role of myeloid cell compartment. We also assess the effects on lipid profile of targeted therapies in RA patients.
3. **Biomarkers to predict the outcome of early inflammatory arthritis.** The long-term outcome of inflammatory arthritis cannot be predicted from the disease's outset. In a cohort of patients with early disease we explore for a molecular "fingerprint" to predict disease's outcome. For that we apply high-throughput technologies (RNAseq, methylomics, glycomics) in peripheral blood cells of patients.
4. **Biomarkers to predict response to biologics in inflammatory arthritis.** Biologic therapies are potent agents with unpredictable response rates up-to 50-60% in patients with RA or spondylarthritides (SpA). In prospective clinical-translational studies we apply combined immunophenotyping and proteomics, in order to identify a molecular "fingerprint" to predict individually clinical responses, in patients starting biologic therapies (TNFα inhibitors, IL-17a) or JAK-inhibitors.

Progress in 2022-2023

- We have characterized the molecular pathway involved in IL-6 mediated immunosuppressive function of Plasmacytoid Dendritic Cells in RA patients responding to TNFα inhibitors. (J Immunol. 2022 Nov 15;209(10):1906-1917)
- In RA patients starting biologic therapy with CTLA4-Ig, we have characterized a signature based on Peripheral Blood Th1 and myeloid cells combined with serum inflammatory mediators, which predicts response to abatacept with a high sensitivity (90%) and specificity (88.24%). (Cells. 2023 Dec 9;12(24):2808)
- Baseline IgG-Fc N-glycosylation profile in early RA patients before starting treatment has been shown to predict long-term outcome in a cohort of early inflammatory arthritis patients. In the same cohort, we finalized transcriptomics' and methylomics' analysis. (Arthritis Res Ther. 2022 Aug 25;24(1):206)
- Well characterized (clinically, laboratory) human cohorts (RA, SpA) are evolving and regularly register in the local registry (UOCRCR), combined to a biobank of serum, peripheral blood immune cells, DNA and RNA. Projects for massive HLA genotyping, whole exome sequencing in subgroups of patients are ongoing.



Web page: https://www.rheumatology-uoc.gr/el/ereunhtiko-ergasthrio

Publications

Goutakoli P, (2023) A Peripheral Blood Signature of Increased Th1 and Myeloid Cells Combined with Serum Inflammatory Mediators Is Associated with Response to Abatacept in Rheumatoid Arthritis Patients. **Cells** 12(24):2808 doi: 10.3390/cells12242808. PMID: 38132128

Papadaki G, (2022) IL-6 Signaling Attenuates TNF-α Production by Plasmacytoid Dendritic Cells in Rheumatoid Arthritis. **J Immunol**. 209(10):1906-1917 doi: 10.4049/jimmunol.2100882. PMID: 36426957

Sénard T, (2022) Baseline IgG-Fc N-glycosylation profile is associated with long-term outcome in a cohort of early inflammatory arthritis patients. **Arthritis Res Ther.** 24(1):206. doi: 10.1186/s13075-022-02897-5. PMID: 36008868

Christos Tsatsanis

Professor - Collaborating Faculty Member

GROUP MEMBERS

Assistant Professor:
Eleni Vergadi
collaborator from the Dept. of Pediatrics, Univ. of Crete

Senior Research Associate:
Eirini Dermitzaki

Postdoctoral researchers:
Maria Daskalaki
Ourania Kolliniati

PhD Students:
Elina Paflioti
Ioanna Pantazi
Ioanna Lapi

MSc Students:
Michaela Gnafaki
Evangelia Kandylaki
until Sept. 2023

Research Fellow:
Avery Hurst

MOLECULAR IMMUNOLOGY & INFLAMMATION

Summary

Mechanisms shaping innate immune responsiveness

Innate immune responses are modified by pathogenic and non-pathogenic stimuli. Macrophages, the central mediator of innate immune responses, obtain different activation phenotypes in the context of metabolic disease, infections and inflammatory diseases. Our work focuses on understanding the mechanisms regulating innate immune responsiveness and how these changes may contribute in disease pathogenesis.

Current aims

Aim of our work is to delineate how insulin, metabolic or inflammatory signals change the responsiveness of macrophages, fibroblasts as well as the differentiation and activation of adipocytes. For our studies we utilize mouse models of inflammation and infection, focusing on bacterial infection and sepsis. How insulin signaling and insulin resistance modulate macrophage responsiveness to infection is being investigated. The lab has long-standing expertise on Akt signaling and the contribution of Akt-mediated signals in innate immunity. The crosstalk of insulin signaling with epigenetic changes at the level of histone methylation that occur in the context of obesity and metabolic disease is currently analyzed. In addition, we study how these changes affect macrophage metabolism and, in turn, responsiveness to inflammatory stimuli.

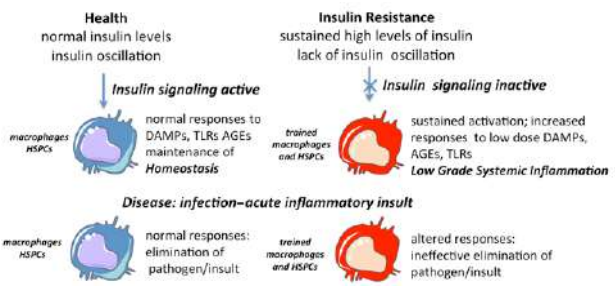
The impact of metabolites and nutritional products on innate immune responses and the gut microbiome is also investigated. Dietary metabolites can either directly or indirectly, via altering the gut microbiome, affect metabolic inflammation, inflammatory diseases and macrophage responses. To this end, using mouse models we are analyzing a series of metabolites and nutritional products on the gut microbiome and how these can modulate inflammatory responses in the context of metabolic and inflammatory diseases.

Progress in 2022-2023

Our group has been analyzing the regulation of innate immune responsiveness and how this is regulated at the epigenetic and signaling levels in the context of trained immunity and innate immunity maturation. We have been studying the contribution of cell metabolism and Akt signaling in regulating responsiveness of macrophages and overall innate immune responses (Curr.Topics Microbiol. Immunol., 2022; J Innate Immun., 2022; eLife, 2023). Along these lines we investigated the role of Akt signaling in bacterial and viral infections, focusing on epithelial cells, another cell type important for the first line of response to infections. We showed that Akt signaling was critical for the effect of SARS CoV2 on lung alveolar epithelial cells and particularly in mediating ACE2-driven signaling that led to production of inflammatory mediators (Front Immunol. 2022).

In collaboration with Assistant Professor E. Vergadi, former postdoctoral fellow of the group, we demonstrated that Akt signaling was also important for the response of alveolar epithelial cells to Streptococcus by promoting autophagy and bacterial clearance (Pathogens, 2022). In addition, we demonstrated that that response to polymicrobial sepsis in neonates is under the control of the cytokine IL-10 and DEL-1 protein, which both regulate granulopoiesis at the level of bone marrow progenitor cells (Nat. Comm. 2024).

Our work also focused on the impact of metabolic and nutritional products in regulating inflammation and the gut microbiome. We showed that nutritional supplementation with hydrolyzed proteins modulates macrophage responses and suppress inflammatory diseases such as metabolic inflammation through changes in the gut microbiome (Mar. Drugs 2023).



The role of insulin signaling and insulin resistance in regulating macrophage responses.

Other activities

We have contributed to the organization of an international conference in collaboration with the International Federation of Clinical Chemistry (IFCC), the European Federation of Laboratory Medicine (EFLM), the Arab Federation of Clinical Biochemistry and the Greek Society of Clinical Chemistry (3rd IFCC, EFLM, AFCB "Laboratory Medicine for mobile societies"), held in Heraklion, 2022, which was under the auspices of IMBB-FORTH.

International fellows visited the lab for one-month training under the EFLM exchange training program-EFLM-LabX (one fellow from Romania and one from Russia). A fellow from Serbia under the MSCA-SE program CardioSCOPE also visited the lab for training.

A research fellow from the USA was awarded the 'Fullbright Foundation' Fellowship to receive training for one year in our lab on evaluating bioactivity of natural products.

We presented our work in national and international scientific conferences receiving one travel award and one scientific excellence award at the "Innate Immunity" Conference organized as part of the "Aegean Conferences."

Web page https://www.imbb.forth.gr/imbb-people/en/tsatsanis-overview

Publications

Mateska I, et al. (2023) Succinate mediates inflammation-induced adrenocortical dysfunction. **Elife**. 12: e83064

Kolliniati O, et al. (2022) Metabolic Regulation of Macrophage Activation. **J. Innate Immun**. 14(1):51-68

Al-Qahtani AA, et al. (2022) SARS-CoV-2 modulates inflammatory responses of alveolar epithelial type II cells via PI3K/AKT pathway. **Front Immunol**. 13:1020624

Panayotis Verginis
Associate Professor
Immunology/Biochemistry

GROUP MEMBERS

Postdoctoral researchers:
Aikaterini Hatzioannou

PhD students:
Athina Varveri
Iosif Papafragkos
Miranta Papadopoulou
Athina Boumpas
Antonis Papaioannou
Efrosyni Markaki
Zacharias Papadovasilakis

Research Assistant:
Lydia Xenou

IMMUNE REGULATION

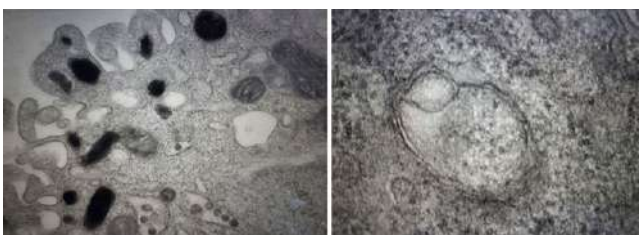
Summary

The research focus of my laboratory is placed on the mechanisms of immune regulation and tolerance with particular emphasis in cancer. The advent of immune checkpoint inhibitor (ICI) immunotherapy revolutionized cancer treatment, underscoring the pivotal role of immune system in cancer eradication. Despite the clinical success, cancer immunotherapy remains ineffective in a large proportion of patients, proposing that **unappreciated mechanisms of resistance exist**. Another major impediment of immunotherapy is the development of immune-related autoimmune events (irAEs) that frequently occur in patients responding to ICI, and suggests an important role of tolerance mechanisms in the balance between ICI-mediated responses and development of irAEs. **Delineating the mechanisms underlying the limited efficacy of immunotherapy and the ensuing autoimmunity is of urgent need in order to design rational therapeutic protocols for cancer treatment but also will facilitate the discovery of predictive biomarkers for personalized therapy.** The research interests of my lab aim to address these unmet needs in cancer field and to understand the immune tolerance mechanisms that operate to limit the anti-tumor immune responses, centred on immune cells with suppressive properties such as regulatory T cells (**Tregs**) and myeloid suppressor cells (**MDSCs**).

Progress in 2022-2023

The main scientific directions of my lab are the following:

- **Decoding the "fragile" phenotype of Treg cells in tumor microenvironment. *Rationale:*** Our findings demonstrate that Treg cell "fragility" promotes tumor regression and induction of anti-tumor immunity (Hatzioannou et al. Nat. Immun. 2020). Guided by Treg cell transcriptomic and epigenetic data we aim to reveal molecular signatures of Treg cell fragility that will be validated in mouse models of cancer.
- **Investigating the contribution of adaptive immune responses in non-lymphoid tissues (adipose tissues-AT) in tumor immune surveillance and immunotherapy resistance. *Rationale:*** Immune responses that take place in "atypic" lymphoid tissues such as the adipose tissues have shown to underlie inflammatory conditions such as obesity and diabetes. Considering that various cancer develop in proximity to adipose tissues and also that obesity has linked to cancer development we envision a cross-talk of adipose tissue with tumor microenvironment which imprint on tumor immunity and on the effectiveness of immunotherapy. Single cell transcriptomics of lymphocytes isolated from adipose tissue and lymph node from tumor-bearing animals combined with adipose tissue transplantation experiments are performed to address our hypotheses.
- **Cancer associated fibroblasts (CAFs) form a synapsis with Tregs to promote tumor development.** This project in under completion, and our data demonstrate that CAFs densely accumulate in tumor bed and are in close contact with and facilitate the proliferation of Tregs promoting tumor growth. Through the use of multiple transgenic and conditional knockout mouse models and time lapse microscopy we reveal the synapsis formation between the two cell populations and via transcriptomic analysis we show autophagy to promote tumor-antigen presentation by CAFs to instruct Treg cell proliferation. Finally, ICH of tumor biopsies from patients with melanoma and colon cancer, validate our results.
- **Generation of an Immune Cell Atlas to understand resistance of immunotherapy responses and development of autoimmune side effects in cancer patients – generation of a "liquid" biopsy *Rationale*:** Diagnostic, prognostic and therapy-monitoring procedures require a tumor biopsy, which is associated with very low compliance and relatively high expense. Furthermore, prediction of autoimmune toxicities remains an unmet need. Considering that multiple new ICIs expected to enter clinical practice the following years, identification of biomarkers for prediction of response and autoimmune side effects are mandatory. To address this, we established collaboration with several oncology units in Athens and Heraklion and have established a biobank of peripheral blood and tumor biopsies from patients with melanoma, lung and urotherial cancer as well as bone marrow samples from lymphoma patients. The aim is to identify immune cell populations (via mass cytometry and transcriptomics) that reliably will distinguish responders from non-responders to immunotherapy.



Autophagy in cancer associated fiborblasts in tumor microenvironemnt

Other activities

- Organization of "Immunology school for clinicians" (https://clinicalimmunology-crete-2023.gr)
- PhD fellowships awarded by ELIDEK to Iosif Papafragkos and Efrosyni Markaki

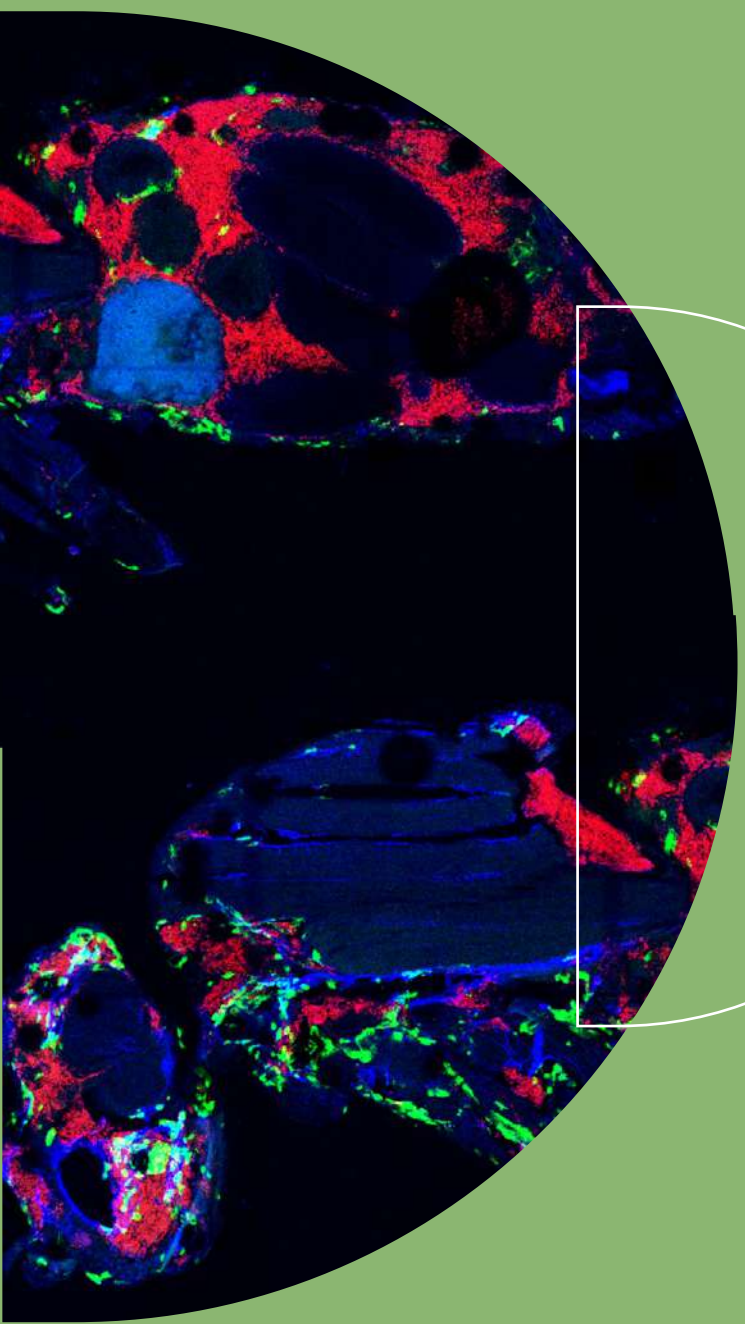
Web page https://www.imbb.forth.gr/el/research-el/item/5972-panayotis-panos-verginis

Publications

Papadaki G, et al. (2022) IL-6 signaling Attenuates TNF-α Production by Plasmacytoid Dendritic Cells in Rheumatoid Arthritis. **J Immunol**. 209(10):1906-1917

Manolakou T, et al. (2022) ATR-mediated DNA damage responses underlie aberrant B cell activity in systemic lupus erythematosus. **Science Advances** 8, eabo5840 doi: 10.1126/sciadv.abo5840

Papafragkos I, et al. (2022) Ablation of NLRP3 inflammasome rewires MDSC function and promotes tumor regression. **Front Immunol.** 13:889075



Evolution, Development & Cell Biology

Christos Delidakis

Professor - Collaborating Faculty Member

GROUP MEMBERS

Senior postdoctoral reseachers:
Vasiliki Theodorou
Evanthia Zacharioudaki
Zoe Veneti

PhD students:
Konstantina Kalodimou
Chrysanthi Voutyraki
Virginia Fasoulaki
Vassiliki Kapoulea

MSc students:
Vasiliki Mpoumpa
Ioanna Soukouli

Research assistant:
Margarita Stapountzi

Undergraduate thesis students:
Evangelia Titaki
Athanasia Stamelou
Anastasia Georgiadi

Marialena Vathi
Anastasia Meligkounaki
Asimenia Goniotaki
Leda Kavallieratou
Myrto Mitletton
George Mandrakis
Christina Thomou

BIOLOGY OF STEM CELLS

Summary

Gene regulation during development, homeostasis and tumorigenesis in *Drosophila*

Somatic stem cells are long-lived undifferentiated precursors of many animal tissues. We study neural and intestinal stem cells in the fruit fly (Drosophila) and how they respond to local signals to modify their gene expression and, consequently, the fate of their progeny cells. Central to our interests is an important signal in the animal kingdom, called Notch. This pathway uses cell surface proteins, the Notch receptor and its ligands, Delta and Serrate, to enable cells to perform contact-mediated transactions with their neighbours. By manipulating Notch signalling we have been able to generate a model cancer in neural stem cells (a.k.a. neuroblasts, NBs), which is the main focus of our work.

Current aims

We use *Drosophila* as a model system to address a number of questions on the integration of signals and epigenetic states with gene regulation in somatic stem cells.

1. We are studying the interplay between proneural transcription factors (TFs) and Notch signalling in the specification and function of neural stem cells (NBs) in the embryo
2. We are studying malignant tumours generated from persistent Notch signalling in NB lineages at the juvenile stage.
3. Neuralized is a ubiquitin ligase, which is needed for sending the Delta signal to Notch. We are studying its interaction with the Delta intracellular domain.
4. The adult Drosophila intestine relies on a population of stem cells (ISCs) to renew its damaged cells. We are investigating the role of epigenetic modification complexes in ISC activity. (with Aris Eliopoulos, Univ. of Athens)
5. We investigate how Notch regulates the expression of the Hey TF during asymmetric cell divisions in the CNS and intestine. (with Maria Monastirioti)

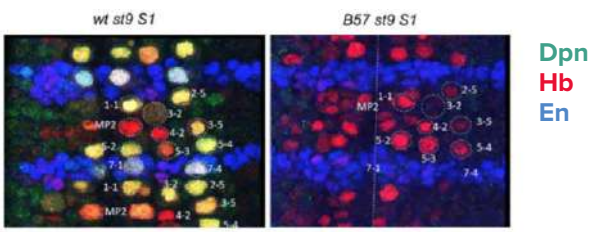
Progress in 2022-2023

We have documented extensive genome-wide binding of proneural TFs in the embryo and characterized some of their target enhancers. Although proneural TFs were thought to be essential for NB specification, we showed that most NBs do form in the absence of proneurals, but their maturation is delayed, their proliferative capacity compromised and their differentiated progeny defective, leading to severe CNS hypoplasia.

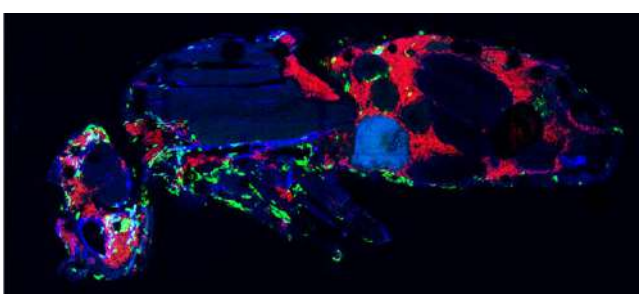
We continued our study of Notch-induced NB tumours in larvae, which we know arise from the de-differentiation of NB progeny. Upon allografting to adult hosts, these tumours spread throughout the body cavity and prematurely kill the host. Adult haemocytes attack and phagocytose tumour cells, in an attempt to curtail its growth. We have used genomic and imaging approaches to gain further insight on the biology of this tumour and its interaction with host haemocytes. (with Angela Giangrande, IGBMC, Strasbourg)

Ubiquitylation of Delta by Neur was thought to be necessary for Delta-Notch signal sending. We showed that the interaction of Neur with Delta is more important than the addition of Ubi molecules per se, which is dispensable for signalling. (with Thomas Klein, Univ. Düsseldorf)

With Maria Monastirioti, we have characterized elements that drive Notch-dependent and Notch-independent expression of the Hey TF. We have documented Notch-dependent Hey expression in the embryonic fly midgut, specifically in one of the two enteroendocrine cells produced by the asymmetric division of their immediate precursor. We currently continue to investigate the functional role of Hey in the determination of cell fates within Drosophila intestine.



In proneural mutant embryos (B57 deficiency, right panel) most NBs form and express the Hb marker (red) but fail to express another neuroblast marker, Dpn (green). En (blue) demarcates segment borders.



Section of a fly containing large numbers of red tumour cells. Note the green haemocytes, phagocytic cells of the host, that cluster near tumour cells.

Other activities

Supervision of the IMBB Confocal and Insect Facilities. Coordination of the Graduate Programme in Molecular Biology and Biomedicine, a joint venture of our Institute with the Departments of Biology and Medicine of the University of Crete. Presentations on developmental genetics to highschool students and newspaper articles.

Web page http://www.imbb.forth.gr/delidakis

Publications

Voutyraki C, (2023) Growth deregulation and interaction with host hemocytes contribute to tumor progression in a Drosophila brain tumor model. **Proc. Natl. Acad. Sci. U S A.** 120(33): e2221601120 doi: 10.1073/pnas.2221601120

Skafida E, et al. (2022) Expression of Hey marks a subset of enteroendocrine cells in the Drosophila embryonic and larval midgut. **Int. J. Dev. Biol.** 66:223-233 doi: 10.1387/ijdb.210203mm

Theodorou V, et al. (2022) ASC proneural transcription factors mediate the timely initiation of the neural program during neuroectodermal to neuroblast transition ensuring progeny fidelity. **BMC Biol.** 20:107 doi: 10.1186/s12915-022-01300-8

Anastasios Pavlopoulos
Principal Researcher (B)

GROUP MEMBERS

Lab Manager:
Marina Ioannou
Postdoctoral Researcher:
Evangelia Stamataki
PhD Students:
Maria Kalogeridi
John Rallis
MSc students:
Themistoklis Archontidis
Eirini-Areti Karapidaki
Ioannis Liaskas
Dimitrios Papageorgiou
Kyriaki-Niovi Rafailidou
Undergraduate thesis students:
Vassilios Flouris
Evangelia Papagrigoraki
Georgios Vlachos
Visiting student:
Nektaria Kokolaki

EVOLUTIONARY DEVELOPMENTAL BIOLOGY & MORPHOGENESIS

Summary

Our Developmental Morphogenesis lab integrates embryological, functional genetics and genomics, in toto imaging and image analysis approaches to understand how animal form and physiology originate and evolve. We use the marine crustacean *Parhyale hawaiensis*, a genetically and optically tractable animal model, that satisfies several appealing biological and technical requirements. First, the *Parhyale* embryo acquires a stereotypic and geometrically ordered tissue architecture, while maintaining the capacity to perfectly restore it after ablation of precursor cells. Second, *Parhyale* develops a series of 19 pairs of serially homologous limbs along its anterior-posterior body axis that differ in size, shape and pattern. And third, *Parhyale* encodes in the genome all enzymes required for autonomous digestion of wood in the absence of symbiotic microorganisms. These qualities offer exceptional material for our studies described below.

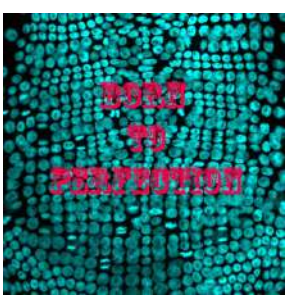
Current aims

Our integrated studies analyze the fundamental units of tissue morphogenesis, the cells, in their native context by reconstructing and comparing high resolution molecular and cellular atlases between sides and limbs in the same embryo and across embryos under wild-type or perturbed conditions. Our fine-grain studies aim to resolve how tissue-level spatial patterns emerge from cell-level properties to generate correctly proportioned body plans. We have also initiated a new research line that involves the multi-omic, genetic and biochemical characterization of the cellulolytic enzymatic cocktails secreted by *Parhyale* for autonomous wood digestion.

Progress in 2022-2023

We have continued expanding the functional genetic, genomic and imaging toolkit for *Parhyale* research. These tools were combined in a number of research lines described below:

1. We have used enhancer bashing to identify the *cis*-regulatory elements controlling the expression of the gene *Distal-less (Dll/Dlx)* in *Parhyale* embryos. *Dll* is a key limb patterning gene with conserved roles in early limb specification and later proximo-distal patterning, but with conflicting evidence regarding the identity of its upstream regulators. Our ongoing characterization of the regulatory logic that initiates, maintains and refines *Dll* expression in *Parhyale* will shed light on the conservation and divergence of the mechanisms driving direct (like in *Parhyale* and most other arthropods) versus indirect (like in *Drosophila* and other holometabolous insects) limb development in pancrustaceans.
2. During *Parhyale* embryogenesis, the ectoderm becomes organized into a highly ordered array of rows and columns of cells. We discovered that during this process, the nascent *Parhyale* ectoderm transitions from a hexagonal honeycomb-like pattern, which is typical for most epithelia, into a lattice of predominantly 4-sided square and rectangular cells. We have imaged and quantitatively analyzed the actomyosin dynamics driving the cell shape changes and cell rearrangement events that occur during this transition. We hypothesize that stalled T1 transitions mediate square cell packing and are currently investigating the cellular and molecular mechanisms that lock cells in this high energy state.
3. We characterized the *Parhyale* cellulolytic cocktail for microbe-free wood digestion. Among cellulose digesters, marine organisms represent promising novel sources for cellulases with superior performance compared to their terrestrial counterparts, but these have remained unexplored due to the scarcity of experimentally tractable marine model organisms. We combined genomics, transcriptomics, proteomics and functional genetic approaches in *Parhyale* to dissect the activity of cellulases in vivo. We are currently overexpressing and purifying these enzymes from *Parhyale* digestive glands and are comparing their kinetic properties against commercially available enzymes in an effort to improve strategies for wood biodegradation of enormous biotechnological value.



Other activities

1. Lecturer and module coordinator in three Master's Programs (Molecular Biology and Biomedicine, Biomedical Engineering, Bioinformatics) and supervisor of 16 postdocs, postgraduate and undergraduate students.
2. Recipient of research grants from the Human Frontiers Science Program, Fondation Santé and the HHMI Janelia Visiting Scientist Program.
3. Host scientist for secondary school visits at IMBB-FORTH and member of IMBB's, FORTH's and EU-LIFE's Gender Equality, Diversity and Inclusion groups.
4. Members of the lab were awarded competitive fellowships for their graduate studies (John Rallis and Kyriaki-Niovi Rafailidou), attended international workshops and conferences, and worked in collaborating labs at the HHMI Janelia Research Campus in USA (John Rallis), the Max Planck Institute of Molecular Cell Biology and Genetics in Germany (Maria Kalogeridi) and the Turing Centre for Living Systems in France (Giannis Liaskas).

Web page https://www.imbb.forth.gr/pavlopoulos

Publications

Cislo DJ, et al. (2023) Active cell divisions generate exotic fourfold orientationally ordered phase in living tissue. **Nature Physics** 19:1201 doi.org/10.1038/s41567-023-02025-3

Tserevelakis GJ, et al. (2023) Hybrid Fluorescence and Frequency-Domain Photoacoustic Microscopy for Imaging Development of Parhyale hawaiensis Embryos. **Photonics** 10:264. doi.org/10.3390/photonics10030264

Rallis J and Pavlopoulos A (2022) Cellular basis of limb morphogenesis. **Curr. Opin. Insect Sci**. 50:100887 doi.org/10.1016/j.cois.2022.100887

Nikos Poulakakis

Professor, Collaborating Faculty Member

GROUP MEMBERS

Senior Postdoctoral Researchers:
Argyro Nafplioti
Nikolaos Psonis
Despoina Vassou

Research assistant:
Eugenia Tabakaki

MSc student:
Sevasti Koursioti
2022-2023

Collaborators:
Pavlidis Pavlos
Collaborating Faculty Member, ICS-FORTH, Associate Professor, Department of Biology, University of Crete

Stamatakis Alexandros
Group Leader of the Biodiversity Computing Group, ERA Chair, ICS-FORTH, Group Leader of Computational Molecular Evolution Group, Heidelberg Institute for Theoretical Studies, Germany, Full Professor at Institute for Theoretical Informatics, Karlsruhe Institute of Technology

ANCIENT DNA PALEOGENOMICS & EVOLUTIONARY GENETICS

Summary

The Paleogenomics and Evolutionary Genetics (PEG) group (Ancient DNA Lab) at the IMBB-FORTH has become a leading source for ancient DNA research and training at a national and international level. In its seven-year history, the group has built a strong network of partners, allowing the international collaboration with other resesearch teams, publish research and provide training opportunities for young graduates.

The mission of the lab is to disentangle evolutionary history using ancient DNA (aDNA), isotopic and bioinformatics methods, with a focus on human archaeology, zooarchaeology, and paleontology in the Eastern Mediterranean region. For this purpose, we apply and develop state-of-the-art ancient DNA analysis methods, multi-isotope approaches, data and computational methods, to investigate questions of population genetics and phylogeography.

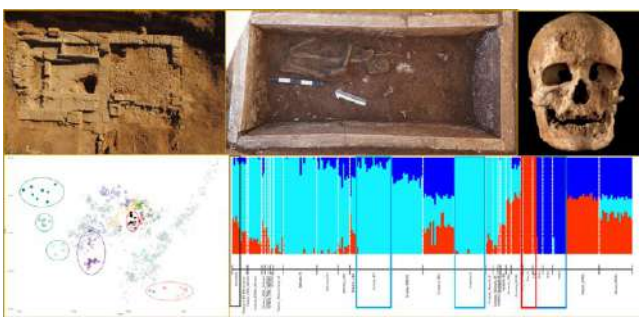
The Ancient DNA Lab research interests span from the evolutionary history of extinct species or lineages with an emphasis on the Mediterranean region, to human evolution, domestication paleogenomics, conservation genomics, and the microbial composition in sediments and ancient remains from humans. Additionally, isotopic analysis of skeletal tissues offers unique insights into past population residential mobility and migration, paleodiet, and the palaeoenvironment.

Current aims

- Genetic profiling and ancestry of Mesolithic Hunter-Gatherers yielding novel insights into the history of mesolithic Aegean.
- Exploration of the genetic relationships among medieval and post-medieval individuals from Crete and other mainland individuals of the same period.
- Genetic profiling of individuals from diverse prehistoric archaeological Greek sites who appear culturally differentiated.
- Investigation of the Neolithic expansion across the Mediterranean and interaction between the Neolithic newcomers and pre-existing populations.
- Investigation of the evolutionary history of extinct mammals, such as Aegean pygmy hippopotamuses or elephantoids.
- Molecular species identification of organisms found in sediments.
- Identification of historical war victims.

Progress in 2021-2023

- Achieved funding from the Hellenic Foundation for Research and Innovation for the project “THESEUS: THe Genomics of the CrEtan population through hiStory and timE, shaping inflammation and immUne homeostasis”.
- Implementation of a project about the identification of 18 executed civilians from World War II in Adele, Rethymnon, following a request from the local community of Adele.
- Implementation of the “Spectra-Gen” project a Theodore Papazoglou FORTH Synergy Grant.
- Implementation of the “NEOMATRIX” project, a three-year-long international scientific collaboration funded by the European Commission’s H2020 grant programme in the framework of the European Twinning instrument.
- Completion of the “APOIKIA” project, an exemplary cooperation between academic, research, cultural heritage institutions and SMEs.



Ancient DNA analysis: From the archaeological field to anchestry and migration

Other activities

- Training of D. Vassou and N. Psonis (2022) in ancient DNA analysis at the Epigenomics & Paleogenomics lab, Université de Paris-CNRS, Institut Jacques Monod, Paris, France.
- Participation of all lab members in several scientific conferences, workshops and program retreats (2021-2023).
- Annual lectures (2021-2023) by N. Psonis “Ancient DNA and applications” in the course “New technologies in Environmental Science, Postgraduate M.Sc. Program of Environmental Biology, Biology Department, University of Crete and the Environmental Course: “Tracing the Past”, Environmental Education Program, 7th High School of Chania.

Web page https://ancient-dna.gr/index.php/en/

Publications

Koptekin D, et al. (2023) Spatial and temporal heterogeneity in human mobility patterns in Holocene Southwest Asia and the East Mediterranean. **Current Biology** 33,1:41-57

Psonis N, et al. (2022) High-throughput degraded DNA sequencing of subfossil shells of a critically endangered stenoendemic land snail in the Aegean. **Molecular Phylogenetics and Evolution** 175:107561

Psonis N, et al. (2022) Mitochondrial sequences of the extinct Cypriot pygmy hippopotamus confirm its phylogenetic placement. **Zoological Journal of the Linnean Society** 196,3: 979-989

Nektarios Tavernarakis

Professor - Collaborating Faculty Member

GROUP MEMBERS

Senior Staff Scientist:
Maria Markaki

Lab Manager/Special Research Assistant:
Angela Pasparaki

Postdoctoral researchers:
Ioanna Daskalaki *left in 2023*
Ilias Gkikas *left in 2023*
Georgios Konstantinidis
Dimitris Korovesis
Eirini Lionaki *left in 2023*
Thanos Metaxakis *left in 2022*
Teresa Rubio-Tomás
Aggeliki Sotiriou

PhD students:
Kostas Kounakis
Mrutyunjaya Panda
Dionysia Petratou *left in 2023*
Dikaia Tsagkari

MSc students:
Manolis Spanoudaki *left in 2023*

Undergraduate thesis students:
Chrysi Athanasiadou *left in 2022*
Magdalini Giannopoulou *left in 2023*
Maria Kalykaki *left in 2023*
Ioannis Tsiamantas *left in 2023*

Visitors and trainees:
Sumeyye Akkaya *left in 2023*
Eva Alegre-Cortes *left in 2022*
Onur Çakici
Sophia Delis *left in 2022*
Giorgos Efstathiou
Stefan Jakovljevic *left in 2023*
Pablo Lavana-Castro *left in 2023*
Efe Semercioglu
Matthaios Sertedakis *left in 2023*
Manolis Stiakakis *left in 2023*

NEUROGENETICS & AGING

Summary

We use the nematode *Caenorhabditis elegans* to elucidate the molecular mechanisms of necrotic cell death and neurodegeneration, the interplay between cellular metabolism and ageing, the mechanisms of sensory transduction and integration by the nervous system, and to develop novel genetic tools for biomedical research.

Current work in the lab aims to:

1. Delineate the crosstalk between dysregulated lipid metabolism and mitochondrial function in neurodegeneration.
2. Investigate the role of the circadian clock in modulating mitophagy and metabolic functions in the context of neuronal degeneration associated with Alzheimer's disease.
3. Elucidate the role of peroxisome biogenesis in polyglutamine-induced toxicity.
4. Characterize novel molecular events that influence the heat shock response in the context of Huntingtin (Htt) protein aggregation in Huntington's Disease.

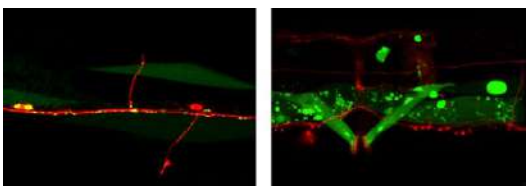
Progress in 2022-2023

Our findings revealed a novel mechanism that relies on metabolic reprogramming to increase longevity. Specifically, we have shown that reducing mitochondrial protein import and consequently mitochondrial abundance leads to lifespan extension. Reduced mitochondrial abundance correlates with reduced reactive oxygen species production, induction of mitochondrial proteotoxic stress response mechanisms and induction of glucose uptake. Metabolic profiling of animals with reduced mitochondrial load reveals a rewiring of cellular glucose metabolism towards de novo biosynthesis of the amino acid serine. Interestingly, inhibition of serine production abolishes the lifespan benefit of mitochondrial depletion, suggesting a causative role for this pathway in longevity. In addition, we have uncovered a critical role for nucleophagy in regulating soma longevity and germline immortality by preserving nuclear architecture and preventing nucleolar expansion. Indeed, nucleophagy has been shown to act as a downstream effector of low insulin/IGF1 signaling and dietary restriction on somatic ageing. Impairment of nuclear material recycling via nucleophagy has been shown to reduce stress resistance, undermine animal longevity and trigger progressive germline mortality. Nesprin family members serve as key regulators of nucleophagy. Using an innovative, non-invasive optical imaging platform developed in collaboration with the National and Kapodistrian University of Athens and the Institute of Electronic Structure and Laser, we have uncovered a novel quality control mechanism that regulates lipid accumulation in the cell nucleus, thereby maintaining cellular and organismal homeostasis during ageing.

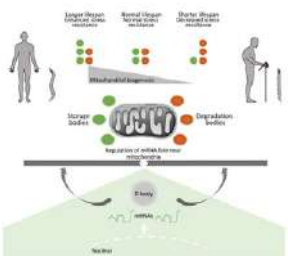
Our efforts to identify new molecular players in the ageing process have revealed that mRNA metabolism determinants play a key role in ageing through the regulation of mitochondrial metabolism and function. Our work has shown that in somatic cells, mRNA degradation and deadenylation complexes form distinct foci that are closely associated with mitochondria. The specific localization of these structures in the vicinity of mitochondria allows the regulation of mRNA transcript fate and consequently influences mitochondrial biogenesis during ageing and under stress conditions. Components of these two macromolecular complexes therefore determine the number and function of mitochondria, modulating lifespan and stress resistance.

The importance of mitochondria in ageing has also been reinforced by our study showing that CISD-1, a mitochondrial iron-sulfur cluster binding protein, serves as a mechanistic link between autophagy and the mitochondrial apoptotic pathway to differentially modulate organismal proteostasis and ageing.

Finally, we defined the crucial role of DEL-4, a proton-inhibited DEG/ENaC ion channel, in maintaining neuronal survival and homeostasis under stress.



Monitoring cellular processes in *C. elegans* transgenic animals *in vivo*.



A working model for the role of mRNA metabolism determinants in ageing and stress resistance, through the regulation of mitochondrial biogenesis and function.

Other activities

- Elected Chairman of the European Institute of Innovation & Technology and Fellow of the European Academy of Sciences.
- Co-organiser of international scientific workshops.
- Keynote and invited speaker at several international conferences.
- Members of the group have been awarded highly competitive fellowships and grants to pursue their doctoral and post-doctoral studies in the lab.
- International collaborations with researchers in the USA and Europe, as well as with industry.
- Establishment of a state-of-the-art super-resolution microscopy unit.

Web page http: www.elegans.gr/

Publications

http://www.tavernarakislab.gr/publications/publications.html

Daskalaki I, et al. (2023) Local coordination of mRNA storage and degradation near mitochondria modulates *Caenorhabditis elegans* ageing. **EMBO Journal** 42: e112446

Papandreou M-E, et al. (2023) Nucleophagy delays ageing and preserves germline immortality. **Nature Aging** 3:34-46

Lionaki E, et al. (2022) Mitochondrial protein import determines lifespan through metabolic reprogramming and de novo serine biosynthesis. **Nature Communications**, 13: 651

Maria Monastirioti
Senior Staff Scientist in collaboration with Christos Delidakis group

NEURAL DEVELOPMENT

Cellular fate and function

Establishment of the characteristic anatomical and functional properties of a cell type is accomplished by the concerted action of internal and external cues. We are interested in the mechanisms that are implicated in intercellular communication and are involved in the determination of cellular fate and function to understand their impact in the physiology and behaviour of organisms. Using *Drosophila* as a model system for our studies, we have previously identified the bHLH-O protein Hey as a transcriptional target and effector of Notch signalling in the CNS during asymmetric division of GMC precursors into two neurons of different fate. In a follow up study, we also documented the Notch dependent expression of Hey in the embryonic fly midgut specifically in one of the two Enteroendocrine cells produced by the asymmetric division of their immediate precursor. We currently continue to investigate the functional role of HeyTF in the determination of cell fates, any putative interactions with other TFs, their transcriptional targets and the gene expression programs they control. We also characterized the genomic regions that support Notch-dependent and Notch-independent expression of the Hey gene and we further investigate its transcriptional and post-transcriptional regulation.

Other activities

Teaching courses in two Graduate Programs of University of Crete (UOC) (“Molecular Biology & Biomedicine”, “Neurosciences”).
Represented IMBB in the organizationof Researcher’s Night event (September 30, 2022) and Co-Organizer of the 1st IMBB Alumni community reunion event (October 20, 2023).

Web page www.imbb.forth.gr/en/research-en/neurosciences/item/72-maria-monastirioti

Maria Markaki
Senior Staff Scientist - Tavernarakis Lab

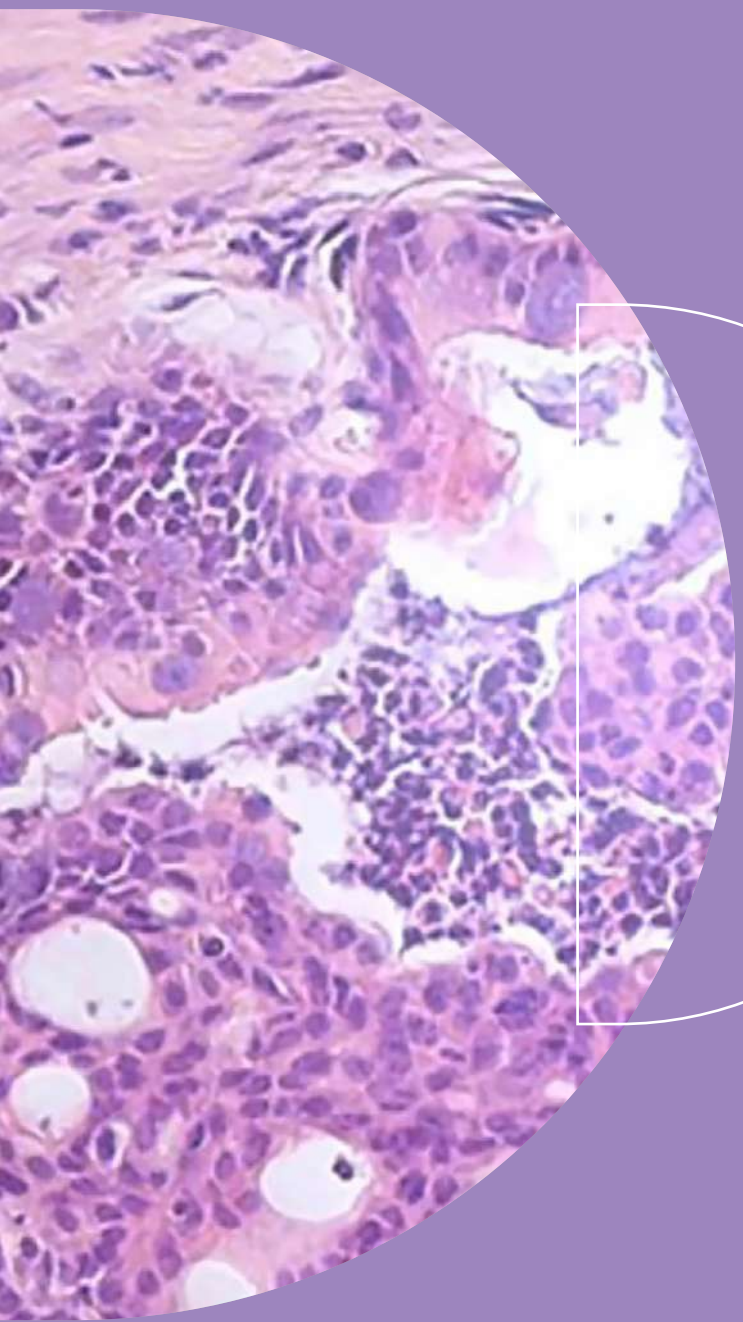
NEUROGENETICS & AGING

Ageing is associated with a decline in physiological function and increased susceptibility to diseases, including neurodegenerative disorders. Although considerable research has been undertaken to elucidate the mechanisms of ageing in model organisms, the cellular and molecular pathways linking ageing and neurodegeneration remain poorly understood. Our current work focuses on investigating the effects of ageing on autophagy and lipid metabolism and how alterations in these pathways may contribute to ageing and age-related neurodegeneration. To achieve these goals, we combine genetics and genomics, molecular biology and biochemical techniques with imaging approaches using the nematode *Caenorhabditis elegans* as a model organism.

Other activities

Coordinator of the course “Principles of Cellular and Molecular Biology”, Postgraduate Programme in Bioinformatics, School of Medicine, University of Crete.
Member of the Gender Equality, Inclusion and Diversity working groups of the IMBB and EU-Life.

Web page https://tavernarakislab.gr/people/maria_markaki.html



Gene Regulation & Epigenetics

George A. Garinis
Professor - Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers:
Georgina Hatzinikolaou
started in 2012
Callina Stratigi
Started in 2016
Evi Goulielmaki
Started in 2016

PhD students:
Alexia Akalestou
Athanasios Siametis
Vivian Kalamara
Giorgos Niotis
Ermioni Arvanitaki
Ioanna Stavgiannoudaki

MSc students:
Manolis Theodorakis
Lab manager:
Kavadina Katrakili

GENOME INTEGRITY, DNA REPAIR, NEUROGENETICS & AGING

Summary

We are using a series of genetically engineered mouse models that carry inborn DNA repair defects or tagged proteins involved in DNA repair or transcription to dissect the impact of DNA damage on mammalian physiology during aging. This approach allows us to understand how mammalian cells exploit their natural defense strategies to counteract DNA damage-driven pathologies and prolong healthspan.

Current aims

Current work in the lab is focused on:

1. **Elucidating the impact of DNA damage on immunometabolism:** Besides genome maintenance pathways, multicellular organisms also employ adaptive and innate immune mechanisms to guard themselves against bacteria or viruses. Recent evidence points to reciprocal interactions between DNA repair, DNA damage responses and aspects of immunity; both self-maintenance and defense responses share a battery of common players and signaling pathways aimed at safeguarding our bodily functions over time. Using the mouse, we are investigating the beneficial and unrewarding outcomes of DNA damage-driven inflammation in the context of tissue-specific pathology, metabolism and disease progression.
2. **Dissecting the functional role of Nucleotide Excision Repair in mammalian development:** How DNA damage triggers the onset of tissue-specific pathology in NER patients and accompanying mouse models remains an intriguing question arguing for tissue-specific responses against deleterious threats. Using an in vivo biotinylation tagging approach in mice and a series of cell type-specific knockout animal models, we try to understand how distinct DNA repair mechanisms are functionally linked to developmental gene expression programs in mammals and how chromatin organizers respond to DNA damage during development or with disease onset.
3. **Delineating the functional links between nucleotide excision Repair and transcription:** Recent work has revealed that proteins in nucleotide excision repair (NER) play distinct roles, including some that go well beyond DNA repair (3). NER factors are components of protein complexes known to be involved in nucleosome remodeling and histone ubiquitination (1), as well as transcriptional activation (2) of genes involved in nuclear receptor signaling, stem cell reprogramming, and postnatal mammalian growth. Using a series of functional genomics, mammalian genetics and biochemical approaches, we are investigating these new mechanisms in relation to the developmental abnormalities and premature disease onset observed in NER syndromes.

Progress in 2022-2023

In 2022, Ermioni Arvanitaki and Evi Goulielmaki showed that upon DNA damage, microglia secrete extracellular vesicles that carry cytoplasmic DNA fragments triggering neuronal cell death and age-related neurodegeneration (PNAS in press).

In 2023, Athanasios Siametis and Callina Stratigi revealed a functional role of TFIIS in telomere attrition with aging (Nature Communications in press). Cumulatively their work allowed the lab to secure two funding programs (HORIZON-WIDERA-2023-ACCESS-04, Hevolution) that will commence in 2024.

Microglia secrete extracellular vesicles loaded with cytoplasmic DNAs leading to age-related neurodegeneration upon DNA damage

Other activities

2022: Organizer, EMBO Workshop on "Developmental Circuits in Aging", Heraklion, May 27-30, Crete.
2022: Launching of Agevio Therapeutics Inc.
2022-23: New funding from 1). Greece 2.0. Flagship actions, 2) FORTH Synergy Grants, 3) ESOF-Liquid Pancreas, 4) ESOF-Panther.
2022-23: Invited talks in 1) the Groningen-Jena Aging Meeting 2023, Groningen **Netherlands**, 2) the EMBL Symposium: The ageing genome: from mechanisms to disease, 4-7 June 2023, Heidelberg, **Germany**, The Pasteur Institute, May 25, 2023, Athens, **Greece**, the 2nd FEBS Workshop "Ageing and Regeneration", Obergurgl, **Austria**.

Publications

Chatzinikolaou G, et al. (2023) XPF interacts with TOP2B for R-loop processing and DNA looping on actively transcribed genes. **Science Advances.** 9(45):1-19

Bujarrabal-Dueso A, et al. (2023) The DREAM complex functions as conserved master regulator of somatic DNA-repair capacities. **Nat. Struct. Mol. Biol.** 30(4):475-488 doi: 10.1038/s41594-023-00942-8

Chatzidoukaki O, et al. (2021) R-loops trigger the release of cytoplasmic ssDNAs leading to chronic inflammation upon DNA damage. **Science Advances** 7(47):1-1

Dimitris Kardassis
Professor - Collaborating Faculty Member

GROUP MEMBERS

Senior research assistant:
Paraskevi Papakosta
Postdoctoral researcher:
Efstathia Thymiakou

PhD students:
Katerina Dalakoura-Karagkouni
Isidoros Axiotis
Maria Laskou
Mariyanna Vinychaki
MSc students:
Asimina Kakale

Undergraduate thesis students:
Despoina Lazaridou

GENE REGULATION & CARDIOVASCULAR DISEASE

Summary

Understanding the genetic basis and the molecular mechanisms of Atherosclerotic Cardiovascular Disease

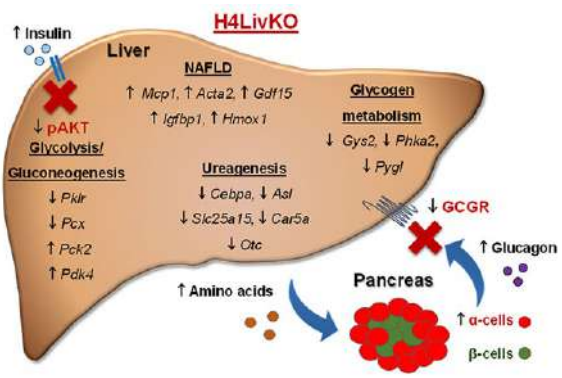
Atherosclerotic Cardiovascular Disease (ASCVD) is the leading cause of death worldwide. Several risk factors including obesity, type II diabetes, non-alcoholic fatty liver disease and dyslipidemia predispose to ASCVD by mechanisms that are not fully understood. Reliable genetic or non-genetic biomarkers are also needed in order to increase the value of current risk prediction algorithms. In our lab we are studying the molecular determinants of atherosclerosis using animal models combined with omics technologies and functional ex vivo studies with the goal to understand better the pathogenesis of atherosclerosis and to identify novel biomarkers and drug targets for ASCVD and other chronic inflammatory diseases.

Current aims

One major aim of our research is the understanding of the molecular mechanisms by which defects in lipoprotein metabolism (high levels of LDL cholesterol and triglycerides, low levels of HDL cholesterol) change the metabolic phenotype of immune cells and contribute to the pathogenesis of autoimmune diseases such as rheumatoid arthritis. A second aim is to understand the role of brain and systemic apolipoprotein E and of metabolic comorbidities (hypertriglyceridemia, NAFLD) on the pathogenesis of Alzheimer's Disease. A third aim is the development of multimarker models for better diagnosis and prediction of Acute Coronary Syndrome (ACS) using multiomics and Artifical Intelligence/ Machine Learning approaches (in collaboration with European partners).

Progress in 2022-2023

- We showed that hypertriglyceridemia in mice, due to the overexpression of the human apolipoprotein C-III gene, changes the metabolic profile of immune cells and compromises HDL anti-oxidant capacity and aggravates rheumatoid arthritis and this effect can be alleviated by lipid lowering therapies.
- We showed that liver-specific ablation of nuclear receptor HNF4A in mice caused α-cell hyperplasia and a dramatic increase in glucagon levels suggesting an impairment of the liver-α-cell axis. In combination with the steatotic phenotype of these mice, our results suggest that H4LivKO mice could serve as a valuable model for studying glucose homeostasis in the context of non-alcoholic fatty liver disease.
- Using adenovirus-mediated gene transfer we provided new insights on the role of specific amino acid residues of apolipoprotein A-I in HDL structure and function and their modification by myeloperoxidase. This knowledge may facilitate the development of novel therapies based on improved HDL forms for patients with chronic diseases that are characterized by dysfunctional HDL.
- We showed that administration of a single dose of reconstituted HDL containing apoE and phospholipids (rHDL-apoE3) in apoE KO mice markedly improved vascular permeability and ameliorated hypercholesterolemia. These novel insights into the rHDL-apoE3 functions suggest a potential clinical use to promote re-endothelialization and retard development of atherosclerosis.



Other activities

- Member of the Management Committee of COST Action CA17129 "Catalysing transcriptomics research in cardiovascular disease" (CardioRNA) (2018-2022)
- Members of the Management and Steering Committees and Leader of Working Group 1 of COST Action CA21115 "Network for implementing multiomics approaches in atherosclerotic cardiovascular disease prevention and research" (AtheroNET) (2022-2026)
- Member of the general Assembly of MCSA-RISE "Comprehensive and personalized assessment of acute coronary syndrome by multiomic approach and artificial intelligence strategy" (CardioSCOPE) (2022-2026)
- Associate Editor of the Journal Atherosclerosis Plus (Elsevier) (2021-today)
- Member of the Organizing Committee of the 2nd Olympiad in Cardiovascular Medicine -International Symposium on Experimental & Clinical Cardiology, Heraklion Greece April 27-30, 2022

Publications

Thymiakou E, et al. (2023) Impaired hepatic glucose metabolism and liver-α-cell axis in mice with liver-specific ablation of the Hepatocyte Nuclear Factor 4α (Hnf4a) gene. **Metabolism** 139:155371 doi: 10.1016/j.metabol.2022.155371

Thymiakou E, et al. (2022) Intestine-specific ablation of the Hepatocyte Nuclear Factor 4a (Hnf4a) gene in mice has minimal impact on serum lipids and ileum gene expression profile due to upregulation of its paralog Hnf4g. **Biochim. Biophys. Acta Mol. Cell Biol. Lipids**. 1867(3):159108 doi: 10.1016/j.bbalip.2021.159108

Valanti EK, et al. (2022) Reconstituted HDL-apoE3 promotes endothelial cell migration through ID1 and its downstream kinases ERK1/2, AKT and p38 MAPK. **Metabolism** 127:154954 doi: 10.1016/j.metabol.2021.154954

Androniki Kretsovali
Research Director (A)

Joseph Papamatheakis
Professor Emeritus-Collaborating Faculty Member

GROUP MEMBERS

Research Technician:
Takis Makatounakis

Postdoctoral Researchers:
Amalia Vogiatzoglou
Fabien Moretto

PhD student:
Sirago Spanou

MSc students:
Dimitra Mitsiadou
Alexandros Minakakis

Undergraduate thesis students:
Stathis Fantidis
Stella Bartzioka
Antzela Zgouro
George Dougalis

GENE EXPRESSION AND CELL FATE REGULATION

Summary

Our lab investigates the mechanisms by which transcriptional, epigenetic and signal transduction factors regulate cell fate. Promyelocytic Leukemia Protein (PML) is a multitasking protein that plays a significant role in cell fate regulation, particularly in the context of cancer biology and cell differentiation. The elucidation of PML functions in normal cell fate decisions is far from complete. In the nervous system, PML functions in brain development, circadian rhythms, plasticity, and the degradation of misfolded proteins. Despite these data, its role in Alzheimer's Disease (AD) has not been studied so far. Our lab focuses in the role of PML in AD pathology employing the mouse 5XFAD model and an acute model of AD via intracerebroventricular (ICV) injection of β-Amyloid (Aβ). In cancer, PML has complex-context dependent-roles by affecting both the cancer cell itself as well its host microenvironment. We study how PML regulates tumor growth and metastasis via multiple pathways that involve cell cycle regulators, epithelial mesenchymal transition and angiogenesis. A third activity of the group concerns the project of Fabien Moretto-our Elidek recipient post-doctoral fellow- on the role of Rpb9 protein in the regulation of cell fate decisions.

Current aims

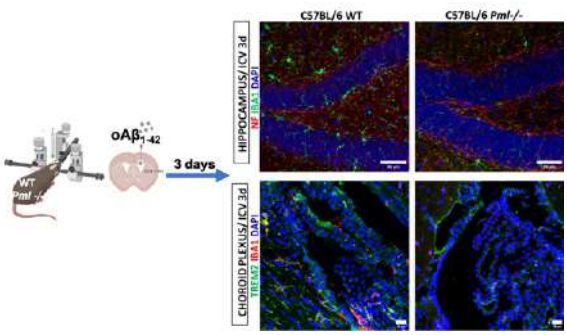
1. Neuronal survival and AD degeneration. We examine the role of PML in neuronal survival and stress response using E13.5 Neural Stem Cells (NSC) originating from WT and *Pml-/-* mice. Functional results are being correlated with transcriptomic and proteomic analyses. To study the role of PML in AD pathology we employ the 5XFAD mouse model and intracerebroventricular (ICV) injection of Aβ.
2. Cancer. We investigate the mechanisms and interplay of cell regulatory factors with oncoproteins in shaping the malignant cell behavior with the long- term goal to develop novel biomarkers and therapeutics. We focus on Breast cancer (BCa) and glioblastoma (GB) models. In collaboration with G. Zacharakis (IESL-FORTH) and V. Sakkalis (ICS-FORTH) we integrate GB-cell physiology and imaging with mathematical modeling to further dissect GB invasiveness.
3. Rpb9/Polr2i: F.M is focusing on the role of the Rpb9 subunit of RNA PolII in the regulation of genes and lncRNAs in yeast. AK is studying the impact of Pol2ri -mammalian homolog of the yeast Rpb9 gene-in mouse embryonic stem cells.

Progress in 2022-2023

1. RNA seq analysis has identified molecular pathways that are deregulated in the absence of PML in eNSC. Major changes were observed in pathways related with mitochondria homeostasis, apoptosis, complement, PDGF signaling and synaptic transmission. We are currently analyzing the impact of distinct pathways' members. Using the 5XFAD mouse model we have observed changes of PML expression correlating with pathology progression. In hippocampi of 6 months old 5XFAD mice (strong pathology), PML is expressed in the cytoplasm of activated microglia cells (Iba positive). Most interestingly using an acute model of AD via intracerebroventricular (ICV) injection of Aβ in WT and Pml -/- mice we have shown that in the absence of PML there is impairment in mounting an anti-inflammatory response and increased neurotoxicity suggesting a role of PML in amyloid clearance and/or the generation of a protective immune response
2. We have combined *in vitro* (cell lines) and *in vivo* (mouse xenografts) studies with RNA seq analysis of parental and PML –KD MDA MB 231 and MCF7 cells. We found that PML loss aggravates the aggressive mesenchymal phenotype of BCa cells and in vivo enhances tumor growth and angiogenesis that result in high metastatic rate. These effects accompany a higher in vitro survival and proliferation of cancer stem cells.

3a. We have shown that Rpb9 has a distinct role in the progression of meiosis and regulates proper chromosome segregation and the efficiency of sporulation. Moreover, Rpb9 regulates gene expression during gametogenesis.

3b. We have employed Crispr/Cas technology to knock down *Polr2* in mouse embryonic stem cells. Pol2ri KO cells were impaired in neuronal differentiation compared to the WT. We have prepared samples from these cells to subject to RNA, TSS and long-read isoforms.



Intracerebroventricular (ICV) injection of oAβ in WT and Pml -/- mice followed 3 d later by hippocampal sections staining with NF, Iba1 and TREM2.

Other activities

Teaching courses in Graduate Programs of UoC: "Molecular Biology and Biomedicine", "Molecular basis of human disease", "Bioethics".

A.K. participated in the organizing committee for the First IMBB Alumni Reunion (October 20th 2023) to celebrate the 40 years anniversary of IMBB.

Web page
https://www.imbb.forth.gr/imbb-people/index.php/en/kretsovali-research-home,
https://www.imbb.forth.gr/imbb-people/index.php/en/papamatheakis-laboratory

Publications

Vogiatzoglou AP, et al. (2023) Promyelocytic leukemia protein regulates angiogenesis and epithelial-mesenchymal transition to limit metastasis in MDA-MB-231 breast cancer cells. **Mol. Oncol.** 17(10):2090-2108 doi: 10.1002/1878-0261.13501

Kokotidou C, et al. (2022) Adenovirus Fibers as Ultra-Stable Vehicles for Intracellular Nanoparticle and Protein Delivery. **Biomolecules** 12(2):308. doi: 10.3390/biom12020308

Vogiatzoglou AP, et al. (2022) Promyelocytic leukemia protein (PML) and stem cells: from cancer to pluripotency. **Int. J. Dev. Biol.** 66(1-2-3):85-95 doi: 10.1387/ijdb.210154av

Matthieu Lavigne
Assistant Researcher (C)

GROUP MEMBERS

Research assistant:
Electra Tsaglioti

PhD student:
Vaios Theodosiou

MSc students:
Konstantinos Kydonakis
Myrto Midlelton
Marianna Stagaki

Ioannis Sampson *jointly w/ Emma Filippidi (IESL)*

Undergraduate thesis students:
Nektaria Kokolaki
Nektarios Belmezos
Nikolaos Vouzounerakis
Maaria-Electra Kontonikou
Stergios Manakas

Ioannis Petrossian
Christos Botos

Visiting student:
Chadmirah Zaratiana
UPEC, Paris

GENOME INTEGRITY & GENE CONTROL MECHANISMS

Summary

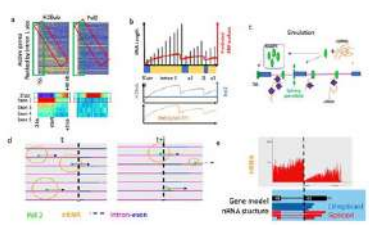
Research interests of my group are centered on the characterization of molecular transactions ruling healthy/disease gene expression programs. To infer transcriptional and epigenetic principles and pinpoint when/how they might go wrong in disease, we need further fundamental understanding of essential chromatin/cellular processes controling RNA polymerase II transcription initiation and elongation at both protein coding- and non-coding- (e.g.: lncRNAs, eRNA) genes. We aim to characterize essential gene regulation and repair models by integrating wet and dry experimental approaches. Generation of cellular and biochemical models of transcription regulation in healthy vs perturbed conditions is achieved after biochemical isolation of chromatin components of interest (RNA Polymerase II, histone modifications), analysis of the sequences of DNA and RNA connected to these and by application of multi-omics strategies and mathematical/bioinformatics approaches to simulate and test most likely gene regulatory networks (GRNs) and molecular mechanisms that rule gene expression specificity. As this approach can inform us on what steps are crucial to drive cells commitment in developmental or pathogenic (de)differentiation lineages, we believe our research is very likely to open new avenues for therapeutics.

Current aims

We apply 4D (time and space) -resolution biochemical and Next Generation Sequencing (NGS) protocols as well as bioinformatics analyses/simulations to decipher gene control mechanisms at the molecular/multi-molecular and cellular/multicellular levels. In particular, we use human cell lines to study genome-wide chromatin accessibility and RNA polymerase II, histones modifications and transcription factors binding patterns on DNA via techniques such as ChIP-seq, ATAC-seq. Further interrogation of protein-DNA- RNA- interactions can identify novel nuclear gene regulatory complexes (IP, RIP, ChIP-western), essential chromosome conformations (4C-seq, HiC) and factors that participate in gene expression and repair. Currently, we focus on nascent vs mature RNA levels/location differences in heathy vs cancer or perturbed cell lines. Location and interactomes of these chromatin components are revealed by techniques such as EU-seq, mRNA-seq, GRID-seq, smFISH, and we use single cell (sc) (scRNA-seq and scATAC-seq) approaches to establish transcriptional and chromatin regulatory networks controlling cellular differentiation trajectories.

Progress in 2022-2023

An outstanding question for understanding gene regulation is what chromatin components participate in genome organization. We propose that nascent RNA (nRNA) is an overlooked component that might interact with chromatin modifier enzymes such as RNF20/40 that ubiquitinates histone H2B. We have also started to investigate how this transient molecule can impact chromatin folding and if it participates in establishing robust gene regulatory pathways that determine cells functions/state. To address these questions, we have generated mutated human hepatocellular carcinoma cells by CRISPR-Cas9 technologies to tag and enable acute depletion of RNF20/40. Efforts to map the effect of nascent RNA can benefit from the opportunity to study the effect of splicing on these elongating chains of RNA (co-transcriptional). We have already me important milestones by applying/developing new tools that enable us to study what exact changes in nRNA-related chromatin composition and interactions occur. In particular, we investigated nRNA and H2Bub and RNF20/40 distributions around the splicing sites by analysing ChIP-seq and correlating it to topology of nascent transcripts revealed by Long reads sequencing (Nanopore or PACBIO). We also designed a computer simulator to predict transcription regulation steps sensibility to various drugs or KO experiments, as well as the effect of splicing on nRNA shape and interactions with chromatin and on RNA polymerase initiation and elongation rates. Finally, we can predict chromosomal interactions effects on gene expression with integrative bioinformatics tools that can predict the functional links between enhancers and target genes. In a collaborative project with Talianidis lab (IMBB) we were even able to analyse gene regulatory rules in mouse intestinal cancer development by implementing single-cell multiomic analyses.



Rationale for the hypothesis of nRNA-dependent H2Bub and possible impact on RNA Polymerase 2 regulation and in silico simulation of nRNA properties around splicing sites

Other activities

1. Scientific head of the Genomics Facility
2. Invited speaker at 2022 10X Genomics USER meeting in Prague, CZ.
3. Teacher in the Master's Program in "Molecular Biology and Biomedicine" of the University of Crete and IMBB-FORTH
4. Together with Dr. Emmanouela Filippidi at IESL-FORTH, we were awarded a FORTH Synergy grant in 2023 to investigate the rules of specificity in chromatin condensates
5. Together with Dr. Iannis Talianidis, we were awarded a HFRI grant in 2023 for Modeling Transcription: an integrated approach to understand cancer- specific gene expression programs
6. Partner lab in the BrainPrecision emblematic action (2023-25)

Web page https://www.imbb.forth.gr/en/research-en/item/5922-matthieu-lavigne

Publications https://pubmed.ncbi.nlm.nih.gov/?term=Lavigne+MD&sort=date

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Liakos A, et al. (2023) Enhanced frequency of transcription pre-initiation complexes assembly after exposure to UV irradiation results in increased repair activity and reduced probabilities for mutagenesis. **Nucleic Acids Research** 51(16):8575–8586 doi.org/10.1093/nar/gkad593

Armaka M, et al. (2022) Single-cell multimodal analysis identifies common regulatory programs in synovial fibroblasts of rheumatoid arthritis patients and modeled TNF-driven arthritis. **Genome Med**. 14(1):78 doi: 10.1186/s13073-022-01081-3

George Mavrothalassitis

Professor - Collaborating Faculty Member

GROUP MEMBERS

Post doctoral researcher:
Angeliki Vogiatzi

PhD Students:
Angeliki Vogiatzi
Aikaterini Vourlia

MSc Student:
Aikaterini Vourlia

Technical Support:
Aikaterini Vourlia
Lydia Xenou

Diploma thesis students:
Athanasios Katsalifis
Amalia Kapsetaki
Dionysia Argyrou
Maria Banou
Dimitris Karagiannis

GENE REGULATION & CANCER PATHOGENESIS

Summary

We are interested in the transcriptional regulation along the RTK – MAPK - ETS, pathway exploring the regulation, control, mechanism of action and developmental contribution of the transcriptional repressor ERF. We postulate that signaling pathways can also quantitatively signal their inactive state through repressors. Thus loss of function of a repressor may recapitulate abnormal activation of the pathway. Interestingly, when an inhibitor/repressor is functionally inactivated rather than eliminated as in the case of ERF, it may be reactivated and ameliorate pathologies associated with pathway activation.

Current aims

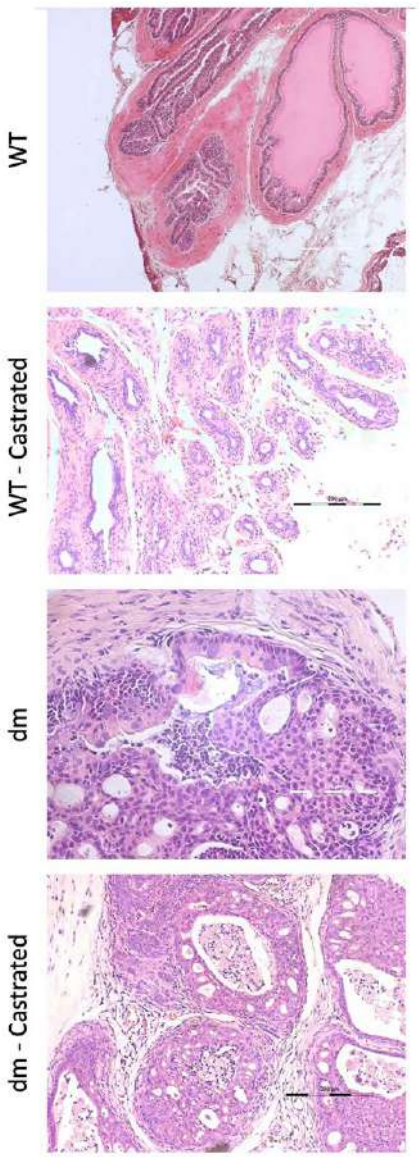
Our goal is to decipher the contribution of the ubiquitously expressed, Mapk-regulated transcriptional repressor ERF in development and disease and explore its potential as a therapeutic target. Erf defects have been shown to lethally affect placenta and hematopoietic embryo development, and lead to syndromic craniosynostosis, Chitayat syndrome, prostate cancer and a yet to be named developmental syndrome. Utilizing cellular and animal models we aim to explore additional Erf-mediated phenotypes, recapitulate the associated diseases and mechanisms of action and expand Erf-targeting pharmacological therapeutic approaches.

Progress in 2022-2023

We developed an several animal model for Erf-induced prostate cancer in mice and currently analyze its similarities with the human disease regarding PCa onset, metastasis and castration resistance with very encouraging outlook. In parallel we evaluate the role and mechanism of ERF contribution in a newly identified myoskeletal and neuronal syndrome that is induced by specific regulatory ERF mutations.

Other activities

Chair of the Division of Basic Sciences of the Medical School of the University of Crete. Chair of the Graduate Studies Oversight Committee at Medical School of the University of Crete. Supervision of the University of Crete confocal facility.



Castration-resistant prostate cancer animal model. H&E staining of the prostates of wild type (WT) and Pbsn-cre;$Erf^{loxP/loxP}$;$Pten^{tm1Hwu/tm1Hwu}$ mice with double prostate specific homozygous elimination of Pten and Erf. Animals were surgically castrated at week 13 and sacrificed at week 25.

Web page http://www.imbb.forth.gr/mavrothalassitis

Publications

Vogiatzi A, et al. (2023) Development of Erf-Mediated Craniosynostosis and Pharmacological Amelioration. **Int. J. Mol. Sci.** 24:7961 2023 doi.org/10.3390/ijms24097961

Tsiomita S, et al. (2022) Ets2 Repressor Factor (Erf) Is Involved In T Lymphocyte Maturation Acting As Regulator Of Thymocyte Lineage Commitment. **J. Leukoc**. Biol. 112:641 doi.org/10.1002/JLB.1A0720-439R

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Evgenia Ntini
Principal Researcher (B)

GROUP MEMBERS

PhD student:
Christos Katsioulas
H.F.R.I Fellow

MSc students:
Nikoleta Pateraki
Sofia Perdikari
Angelos Kozonakis

EPIGENETICS, RNA BIOLOGY & GENE REGULATION

Summary

Research in our group is focused on understanding mechanisms of co-transcriptional RNA processing, with a particular interest on long non-coding RNAs (lncRNAs) transcribed from enhancers. By applying nascent RNA transcriptomics, wet-lab approaches and computational modeling, we aim to characterize differential modes of lncRNA processing and their impact in regulation of gene expression. Unraveling the role of specific RNA-binding proteins, and how epitranscriptomic components, like RNA modifications and their interacting proteins, influence the association of lncRNAs with chromatin is critical in order to characterize deregulation in disease and identify therapeutic targets.

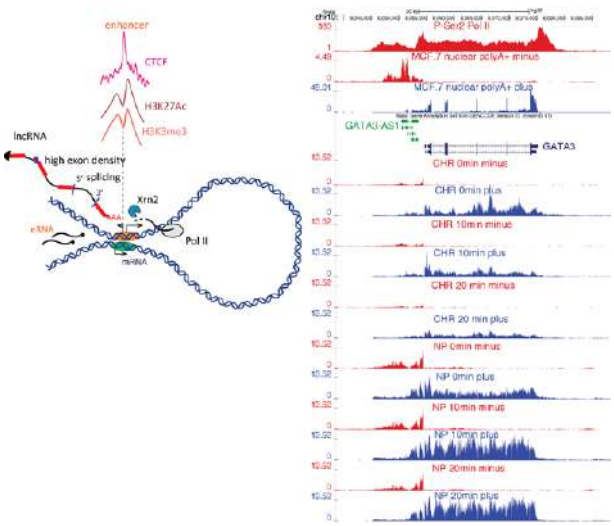
Current aims

Building on our genome-wide analysis[1], we focus our work on validating the role of specific RNA-binding proteins in chromatin dissociation dynamics and co-transcriptional processing of enhancer-transcribed lncRNAs. Furthermore, we aim to characterize the function of a specific RNA modification protein reader in crosstalk with transcription dynamics in response to DNA damage in human cells. Through large-scale bioinformatics analysis of transcriptomic data and computational modeling we aim at uncovering differential modes of lncRNA splicing in clinical samples leading to high-confidence patient subgrouping and identification of transcriptomic biomarkers and therapeutic targets.

Progress in 2022-2023

- We established a novel method for genome-wide measurement of chromatin dissociation dynamics of nascent (aka. newly transcribed) RNA transcripts[1]. Utilizing machine learning and multi-omics data integration, we identified key molecular features, including splicing and specific chromatin states, underlying chromatin dissociation of enhancer-transcribed lncRNAs[1].
- By integrating RNA-binding protein (RBP) binding propensities into machine learning models, we pinpointed at specific RBPs critical for chromatin dissociation of lncRNAs. We have established stable cell lines for dTAG-mediated acute protein depletion and functional validation of prominent RBP candidates (Nikoleta Pateraki, MSc Thesis UoC 2023).
- We have implemented a CRISPR-mediated artificial splicing system to modulate splicing of nascent RNA transcripts and examine the impact on their chromatin dissociation dynamics (Sofia Perdikari, MSc Thesis UoC 2023).
- We have established protocols for direct cDNA sequencing utilizing Oxford Nanopore Technologies, coupled with metabolic labeling and chromatin fractionation, to characterize the linkage between co-transcriptional processing (splicing efficiency dynamics) and chromatin dissociation dynamics of alternative splicing isoforms from the same locus, at a single-molecule level, by employing long-read sequencing (in collaboration with Dr. Despoina Vassou, Research Associate).

Our research has been funded by a Fondation Santé Research Grant, and an H.F.R.I. PhD fellowship to C. Katsioulas.



Other activities

- Supported by an RNA Society grant, we organized monthly RNA salons with invited speakers, and the inaugural Cretan RNA Workshop (2023). Details: https://www.rnasociety.org/current-rna-salons, Twitter@CretanRna
- MSc student Angelos Kozonakis received a travel grant for NG-School2023 in Warsaw, focusing on Advances in Computational Biology.
- MSc student Nikoleta Pateraki was awarded a full travel and accommodation grant for the International Summer School (ISS) on Epigenetics & Genome Stability in Health, Ageing & Disease in Mainz.
- The PI was an invited speaker at two national conferences (HSCBB 2022, Alexandroupolis and HSBMB 2022, Patras) and at IBMiB Poznan.
- The PI participated as a mentor in the EU-LIFE Mentorship programme.

For more information, please visit our webpage: ntinilab.com

Web page https://www.imbb.forth.gr/ntini

Publications

Ntini E*, et al. (2023) Genome-wide measurement of RNA dissociation from chromatin classifies transcripts by their dynamics and reveals rapid dissociation of enhancer lncRNAs. **Cell Syst.** 14(10):906-922.e6. doi: 10.1016/j.cels.2023.09.005 *Co-correspondence

Cortazar MA, et al. (2022) Xrn2 substrate mapping identifies torpedo loading sites and extensive premature termination of RNA pol II transcription. **Genes Dev.** 36(19-20):1062-1078 doi: 10.1101/gad.350004.122

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Charalampos Spilianakis

Professor - Collaborating Faculty Member

GROUP MEMBERS

Special Research Assistants:
Manuela Kapsetaki
Deppie Tsoukatou
Panagiotis Papadopoulos

PhD students:
Tomas Zelenka
George Papadogkonas
Dionysios-Alexandros Papamattheakis

MSc students:
Antonis Klonizakis

Diploma thesis students:
Eleftherios Morres
Michaela Gnafaki
Marianna Verykiou
Konstantinos Vagias
Georgios Zorbas
Anna Piperaki
Ermioni Papanikolaou
Marina Kalaitzaki

EPIGENETICS, CHROMATIN BIOLOGY & GENE EXPRESSION

Summary

The Spilianakis Lab focuses on a range of research areas centered around the immune system, particularly examining the three-dimensional structure of chromatin and its impact on gene expression in the innate and adaptive immune systems. Their main objective involves using a combination of techniques such as biocomputing, molecular biology, biochemistry, imaging, and genetics. These methods are employed to identify and characterize protein complexes that are involved in creating and maintaining long-range chromatin interactions in cells of the immune system.

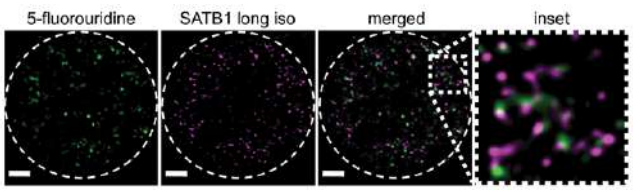
Current aims

A significant aspect of their research is understanding the regulation of high-order chromatin organization in T cells and its implications in autoimmunity. They study the role of the three-dimensional organization of chromatin in gene expression regulation, particularly focusing on the factor CTCF and the special AT-rich sequence binding protein 1 (SATB1), which is a key genome organizer in developing T cells.

The lab also investigates the non-coding RNA-dependent regulation of the immune system, looking into how higher-order chromatin organization influences genome activity and gene expression. This involves studying the spatial positioning of gene loci and how changes in nuclear architecture can lead to diseases. The lab employs various methodologies including mouse models, imaging, computational modeling, and biocomputing to advance their research in epigenetic mechanisms of gene expression regulation within the immune system.

Progress in 2022-2023

An outstanding question for understanding how the immune system functions is how chromatin is organized in three dimensions, what factors are responsible for generating or maintaining this loopscape structure and how gene regulatory pathways are formed to support the (patho)physiological onset of several processes. In the years 2022 and 2023, the SpilianakisLab continued to make significant contributions to the field of immunology and chromatin organization. Some of their notable publications during this period include research on the complex interplay between genomic loci, primary transcripts, and nuclear factors in T cells, providing valuable insights into gene expression regulation at the single-cell level. Another study delves into the intricate relationship between 3D genome organization and its role as an epigenetic factor in regulating transcription in T cells. Moreover, the critical role of SATB1 in shaping the 3D enhancer network of T cell genomes, providing a deeper understanding of T cell development and function was highlighted. These publications demonstrate the lab's continued focus on exploring the complex dynamics of gene expression regulation, particularly in the context of the immune system. Their research is characterized by a multidisciplinary approach, utilizing cutting-edge techniques in biocomputing, molecular biology, and imaging to unravel the mysteries of chromatin organization and gene expression.



STED microscopy indicating that SATB1 speckles co-localize with sites of active transcription. Conclusions were additionally validated by the 3D-SIM approach. Scale bar 1 μm (from Zelenka et.al. 2023).

Other activities

Invited speaker at Cancéropôle Grand Sud-Ouest, Genome Dynamics and Cancer, September 15-16 2022, Toulouse, France.

Web page: www.spilianakislab.gr

Publications:

https://pubmed.ncbi.nlm.nih.gov/?term=spilianakis&sort=date

Zelenka T, et al. (2023) A novel SATB1 protein isoform with different biophysical properties. **Front. Cell Dev. Biol.** 11:1242481 doi.org/10.3389/fcell.2023.1242481

Salataj E, et al. (2023) Single-cell detection of primary transcripts, their genomic loci and nuclear factors by immuno-3D RNA/DNA FISH in T cells. **Front. Immunol.** 14:1156077 doi.org/10.3389/fimmu.2023.1156077

Zelenka T, et al. (2022) The 3D enhancer network of the developing T cell genome is shaped by SATB1. **Nat. Communications** 13(1): 6954 doi.org/10.1038/s41467-022-34345-y

Constantine A. Stratakis
Professor – RESEARCHER A'

GROUP MEMBERS

Post-Doctoral Researchers:
Dr. Elena Vorgia
Dr. Erik Thomas Lundasen

Visiting Researchers:
Dr. Evi Xekouki
University of Crete, Endocrinology
Dr. Kyriaki Bakirtzi
ELPEN, Athens LifeTech Park

HUMAN GENETICS & PRECISION MEDICINE

Summary

Endocrine tumor genetics, protein kinase A, and precision medicine

Our research group aims at connecting basic science in human genetics to phenotypic traits and diseases and potentially use this information for developing medical treatments. As such, we are unique within IMBB and ITE and want to play a central role in the translation of basic to medical science, precision medicine in particular, using the tools and models of molecular biology. Among our many molecular genetic findings, one pathway emerged repeatedly, as linked to predisposition to a variety of phenotypes: that of protein kinase A (PKA), also known as cAMP-dependent protein kinase. We identified inactivating mutations of PRKAR1A, the gene that codes for regulatory subunit type 1A (RIα) of PKA, in patients with Carney complex. In 2014, we and others described defects in PKA's main catalytic (Cα) subunit, PRKACA, in cortisol-producing lesions of the adrenal gland and we identified mosaicism for amplification of the second most important PKA catalytic (Cβ) subunit, PRKACB, causing CNC. Our studies suggested that other PKA subunits could also be involved in other phenotypes. In addition, we identified genes such as GPR101, an orphan G-protein coupled receptor (GPCR) as responsible for growth-hormone producing pituitary tumors and X-linked acrogigantism (X-LAG).

We developed the first animal models that showed PKA's role in tumor development: the conditional knock-out (KO) Prkar1a mouse that we established in 2005 is still being used by laboratories around the world for studying tissue-specific effects of PRKAR1A deficiency. The Prkar2a KO mice that had been made previously were found to develop hematopoietic neoplasms, but also a fascinating metabolic phenotype associated with failure to gain weight, after high fat diet. We focused on Prkar2a and the habenula (Hb). Prkar2a has minimal expression in brain, except for within Hb. We discovered that the Prkar2a KO mice showed decreased consumption of palatable foods and an increased motivation for voluntary exercise.

This work links well with our efforts to identify new tests for diagnosing human tumors, at our genetics unit (DIGENIA, www.digenia.gr) and the unit coordinating the Hellenic Network for Precision Medicine in Molecular Oncology (EDIMO, www.edimo.gr)

Current aims

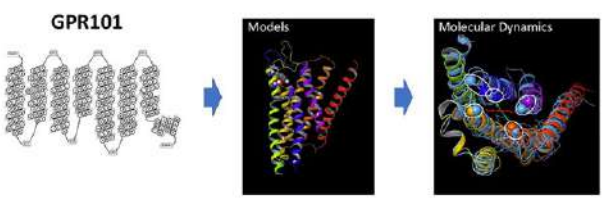
We aim at closing the gap between what is known molecularly and from animal studies and certain human phenotypes, while at the same time proposing compound screening for molecules that regulate PKA function.

Another active project is to identify ligands of the orphan GPCR, GPR101. This is done collaboratively with our collaborators in United States (Dr. Stefano Costanzi, American University, Washington, DC) and in Italy (Dr. Giampaolo Trivellin, Humanitas University, Milano).

Finally, at DIGENIA (www.digenia.gr) and EDIMO www.edimo.gr), a program funded by the European Commission's Recovery & Resilience Facility (RRF), we promote research on new genetic and other testing to identify tumor markers that can be used for the diagnosis, therapy and follow-up of patients with neoplasms.

Progress in 2021-2023

- We identified new variants in the PKA pathway linked to paediatric obesity.
- We identified *PAM* gene variants as a cause of human pituitary tumors.
- FOXD3 genetic and epigenetic changes were found to be involved in the genesis and progression of human gastrointestinal stromal tumors.
- New clinical aspects of Cushing syndrome were published.
- In silico research led to new aspects of potential ligands for GPR101 (see figure and its legend)
- Funding for DIGENIA and EDIMO was secured (https://greece20.gov.gr/?decisions=apofasi-entaxis-toy-ergoy-sub-3-efarmos-meni-ereyna-stin-iatriki-akriveias-meso-enos-organismoy-nomikoy-prosopoy-idiotikoy-dikaioy-idryma-technologias-ereynas-i-t-e-elliniko-diktyo-moriakis-ogkologias). The program is now getting its first samples to be tested



GPR101 is a G protein-coupled receptor (GPCR) implicated in a rare form of genetic gigantism known as X-linked acrogigantism, or X-LAG. GPR101 is a constitutively active receptor, which stimulates cells to produce the second messenger cyclic AMP (cAMP) in the absence of ligands. GPR101 was recently reported to constitutively activate not only the cAMP pathway via Gs, but also other G protein subunits (Gq/11 and G12/13). In our most recent study, we provided structural insights into the putative structure of GPR101 based on in-house built homology models.

Other activities

- Dr. Constantine Stratakis was elected Editor-in-Chief of HORMONES, the highest impact, Greek-edited biomedical journal (impact factor 2023 of 3.2) and the official journal of the Hellenic Endocrine Society.
- Dr. Constantine Stratakis was selected to deliver one of the main plenaries at the European Congress of Endocrinology in May 2024, in Stockholm, Sweden: "From molecular biology to precision medicine in endocrine tumors: Are we there yet?" (https://www.ese-hormones.org/media/cy0oeqn4/ece-2024-preliminary-programme-proof-6-g.pdf).

Web page: www.imbb.forth.gr/en/research-en/item/5891-constantine-stratakis, www.edimo.gr, www.digenia.gr

Publications

Trivellin G, et al. (2023) Germline loss-of-function PAM variants are enriched in subjects with pituitary hypersecretion. **Front Endocrinol (Lausanne)** 14:1166076. doi: 10.3389/fendo.2023.1166076

Costanzi S, et al. (2023) GPR101: Modeling a constitutively active receptor linked to X-linked acrogigantism. **J. Mol. Graph. Model**. 127:108676. doi: 10.1016/j.jmgm.2023.108676

Bloyd M, et al. (2023) High-frequency variants in PKA signaling-related genes within a large pediatric cohort with obesity or metabolic abnormalities. **Front Endocrinol (Lausanne)** 14:1272939 doi: 10.3389/fendo.2023.1272939

Iannis Talianidis
Research Director (A)

GROUP MEMBERS

Post-doctoral researchers:
Haroula Kontaki
Marina Koukaki

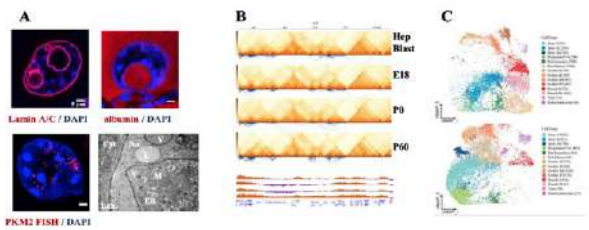
PhD students:
Ourania Galanopoulou
Evaggelia Tachmatzidi
Dimitris Botskaris

CHROMATIN & CANCER EPIGENETICS

Summary
Normal biological functions in a multicellular organism rely on intricate orchestration of the basic cellular features preset by genetic constitution and a sophisticated network of cellular gene expression patterns, which are governed by epigenetic regulation. Epigenetic phenomena refer to the establishment of heritable changes in gene expression without alterations in primary DNA sequence. They impact on many physiological and pathological processes, including aging, metabolism and carcinogenesis. Our research focuses on epigenetic mechanisms regulating liver development, hepatic metabolism and liver cancer pathogenesis.

Current aims
Understanding the role of epigenetic regulatory mechanisms in the stemness characteristics of existing adult progenitor cells and those generated via de-differentiation of adult hepatocytes, is at the center of our current research interest. In particular, we aim at gaining deeper insights into the mechanism of transcription-coupled processes that regulate cellular differentiation and de-differentiation during metabolic stress, cancer initiation and tissue regeneration.

Progress in 2022-2023
Our previous work on transcription factor binding dynamics during liver development revealed that both temporally stable and dynamic, short-lived binding events, as well as progressive broadening of active chromatin domains contribute to the developmental maturation of active promoter configurations. Subsequently, we found that developmental gene activation is also dependent in region-specific changes of 3D genome structure, including A/B compartment switches, TAD reorganization and loop-domain distributions.
A "non-genic" function of the chromatin was discovered by our analysis of Setd8-deficient mice, where the majority of the hepatocytes are eliminated by necrosis, while surviving cells enter into a senescence stage. Senescent hepatocytes had enlarged nuclei, chromosomal hyperploidy and nuclear engulfments progressing to the formation of intranuclear vesicles surrounded by nuclear lamina. These vesicles contain glycogen, cytoplasmic proteins and even entire organelles. We term this process "endonucleosis". Endonucleosis and hyperploidization are temporary, early features of senescence. Larger vesicles brake down into microvesicles over time and are eventually eliminated. The results revealed unique features of senescence phenotype, which function as part of survival mechanisms to prevent necrotic death.
In collaboration with Celia Martinez-Jimenez lab at Hemholtz Centrum, Munich, we have completed a comprehensive study to obtain molecular level understanding of the role of the heterochromatin regulator Setdb1 in the differentiation potential of adult progenitor cells. Our scRNA-seq data revealed that Setdb1 controls proper intestinal epithelial cell fates and a high level plasticity of epigenomes regulating the inter-conversion potential of progenitor and differentiated cell types.



A) Hyperploidy in Setd8-KO hepatocytes. Endonucleosis-generated vesicles, containing cytoplasmic proteins and organelles. B) Examples of TAD reorganization and compartment switches in developmentally activated gene regions. C) Progenitor cell-specific inactivation of Setdb1 leads to abnormal differentiation of intestinal epithelial cell types.

Other activities
- Members of the lab contributed to the development and testing new experimental approaches in IMBB facilities.
- Hosted undergraduate and rotation students for training.
- The PI served as member of ESETEK (National Council for Research and Innovation).
- Presentations in AXA Research Fund events and other international workshops.

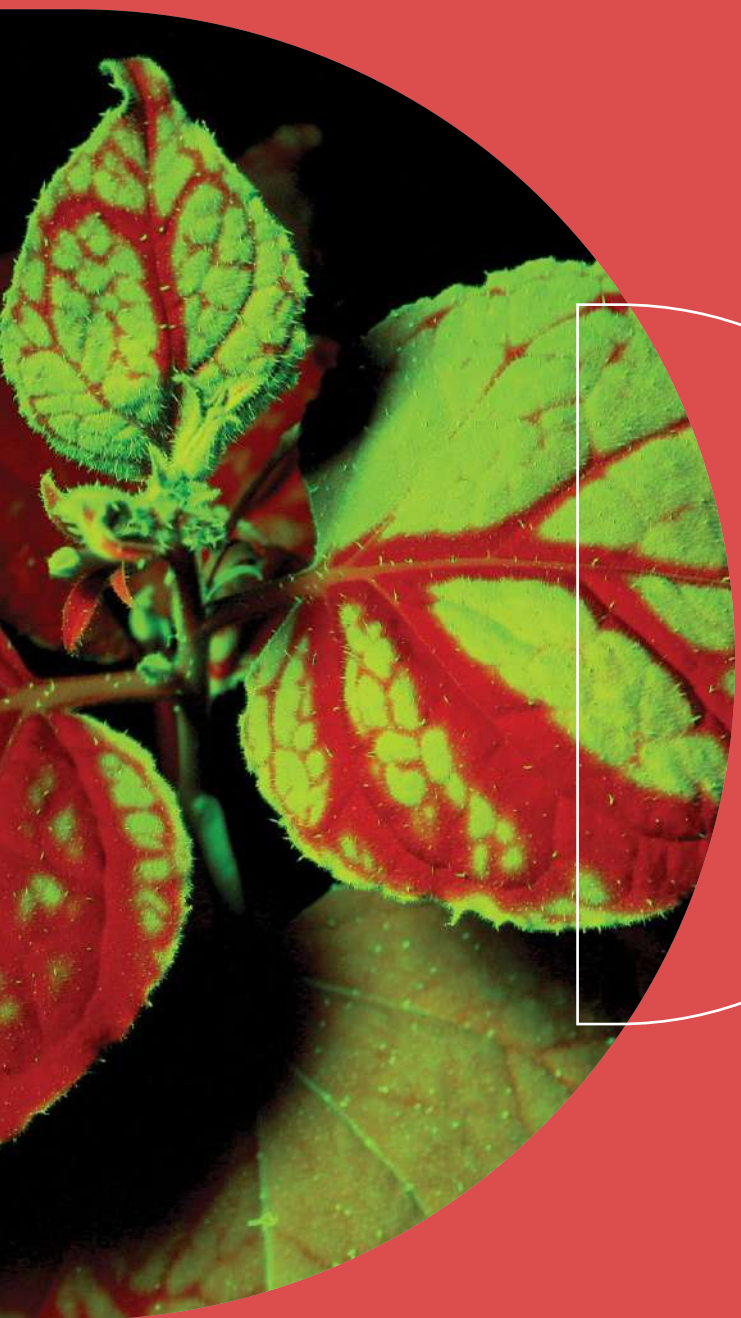
Web page https://www.imbb.forth.gr/imbb-people/en/talianidis-overview

Publications

Galanopoulou O, et al. (2023) Endonucleosis mediates internalization of cytoplasm into the nucleus in senescent cells. **bioRxiv** doi. org/10.1101/2023.11.12.566736

Kontaki H, et al. (2021) Targeting Smyd3 by next-generation antisense oligonucleotides suppresses liver tumor growth. **iScience** 24:102473

Tachmatzidi EC, et al. (2021) Transcription Control of Liver Development. **Cells** 10:2026. (Review article)



Plant & Plant-Microbe Biology

Kriton Kalantidis

Professor - Collaborating Faculty Member

GROUP MEMBERS

Senior research assistants:
Konstantina Katsarou

Postdoctoral researchers:
Nikoleta Kryovrysanaki

PhD students:
Eirini Bardani
Paraskevi Kallemi
Martha Tselika

MSc students:
Andreas Mattos
until 2023
Zoi Pentheroudaki
until 2023
Gemeliari Petroula
until 2022

Undergraduate thesis students:
Aretaki Eleni
2022
Stavroula Papadaki
2022
Konstantina Papastamataki
2023
Dimitrios Paizis Radojkovits
2023

PLANT BIOLOGY & RNA BIOLOGY

Summary

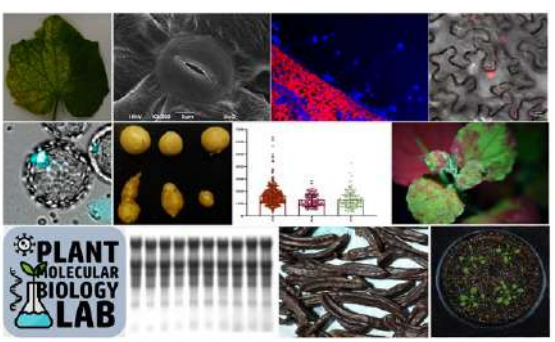
Our main interests include mechanistic aspects of RNA silencing, such as understanding the roles of individual proteins, investigating the cross-talk between RNA silencing pathways and RNA pathogens and evolutionary aspects of silencing. We are also investigating different aspect of the biological cycle of various pathogens emphasizing in viroids.

Current aims

1. Decipher mechanistic and evolutionary aspects of RNA silencing, primarily, but not exclusively in plants.
2. Investigating key steps of viroid biological cycle such as replication and cell-to-cell movement.
3. Functional characterization of Acetyl CoA carboxylase (ACCase) mutations as a case study of differential tolerance to pesticides.
4. Understand Carob genetics and genomics
5. Examine the amplitude of viruses and viroids existing in nature (focusing on the island of Crete)
   - We aim to further our understanding of the role of main components of RNA silencing in Nicotiana benthamiana, especially in relation to viral and viroid infections. We have created tools (by RNAi and CRISPR/Cas9 technology) to study different aspects of their biology. Further, we aim to characterize Non-Dicer proteins.
   - Since viroids rely fully on host factors for the completion of their biological cycle, to understand viroid biology it is important to isolate and charachterise the host interacting factors.
   - Acetyl CoA carboxylase, traditionally a herbicide target, has also become an insecticide target. Our goal is to demonstrate that a single amino acid substitution, unique in plants and insects can alter the selective toxicity of pesticides. This change could make plants resistant to herbicides and susceptible to insecticides but also offer a new selection marker for transforming monocot plants.
   - Having sequenced the first Carob genome, we now aim to re-sequence specific wild and cultivated genotypes. In addition, we are working on evolutionary and biochemical aspects of the Carob genome.

Progress in 2022-2023

1. We have unveiled a diverse DCR/AGO/RDR repertoire in *Phaeodactylum tricornutum*, a very important diatom. DCR knockouts were generated and their mRNA/siRNA transcriptomes were characterized through sequencing, showing a drastic reduction in sRNAs mapping to transposable elements and a concomitant transcriptional activation of TEs.
2. Our research team has detected several novel viral strains and some previously known ones that were first reported in Greece. These findings may have significant implications for the agricultural sector in Crete, as they may pose a threat to the crops and livestock.
3. We have identified specific viral/viroid combinations where the presence of one pathogen affects the levels of the other. We have also identified a combined effect of satellite RNAs and their respective helper virus against the silencing machinery.
4. We have performed intensive bioinformatic analysis and combined it with Mass Spectrometry data and concluded that the small open reading frames found on viroids sequences are not used for translation but only for ribosomal binding.
5. We have shown that VIRP1 as a host factor substantial for viroid replication. We have new insights on its endogenous role as a transcriptional regulator and our new data shed light onto the specific role of VIRP1 in the viroid biological cycle.
6. We have identified 5 RTL proteins in *N. benthamiana* and we are working in understanding their possible involvement in viroid replication, but also their role for the plant itself.
7. In order to understand the interplay between viroids and DNA methylation we have performed a series of experiments including MSAP-Seq and identified that the overall methylation status of *N. benthamiana* upon viroid infection.
8. We have sequenced for the first time internationally the genome of a cultivated Carob tree from Crete. The genome of approximately 500 Mb was sequenced with a 100X coverage resulting in a high quality assembly at chromosome level.



Selected impact activities

- Attendance at “Researchers Night” to interact with public via hands-on experiments with plants.
- Hosting the ‘Viroids, viroid-like RNAs and RNA viruses’ meeting. (Heraklion 14-16 September 2022)
- Secondary school visits to discuss Biotechnological research in plants.
- Undertook regional activity for the advancement of Carob research

Web page https://www.imbb.forth.gr/imbb-people/en/kalantidis-laboratory

Publications https://www.imbb.forth.gr/imbb-people/en/publications-kalantidis

Tselika M, et al. (2023) PSTVd infection in Nicotiana benthamiana plants has a minor yet detectable effect on CG methylation. **Front Plant Sci.** 14:1258023

Bardani E, et al. (2023) Spotlight on Plant Bromodomain Proteins. **Biology (Basel)** 12(8):1076. doi: 10.3390/biology12081076

Katsarou K, et al. (2022) Revisiting the Non-Coding Nature of Pospiviroids. **Cells** 11(2):265. doi: 10.3390/cells11020265

Panagiotis Moschou
Associate Professor - Collaborating Faculty Member

GROUP MEMBERS

Technical Assistant:
Maria Papadovasilaki
Athanasia Christopoulou

PhD students:
Andriani Mentzelopoulou
Ioannis Chatzianestis
Fanourios Mountourakis

MSc students:
Kyriakos Mavridis
Petrpoula Leventaki

Undergraduate thesis student:
Ariadni Siopi

PLANT EPIGENETICS & MOLECULAR PHYSIOLOGY

Summary

Work in our group focuses on the roles of protein and RNA homeostasis in the development and perception of the environment. We are particularly interested in how proteins and RNA forms dictate the basic biological processes of stem cell fate regulation and regeneration. In our research, we mainly use the model plant Arabidopsis but we also use crop models such as rapeseed and tomato.

Current aims

We investigate how RNAs and proteins form new assemblies that can resemble liquid droplets and how they affect molecular and organismal outcomes. Through our models, we aim to further establish the role of the cell shape, geometric edges, and peptides regulating cell fate and development in plants. We recently succeeded in the development of *in vitro* reconstitution systems that allowed us to study all these processes at single-molecule resolution. We exploit advanced imaging approaches, omics, biophysics, single-molecule dynamics, and structural data (main focus on prion-forming proteins) to build holistic models. Furthermore, the development of applications based on the aforementioned processes in crop improvements is on the way.

Progress in 2022-2023

We established a proximity biotinylation system by which signaling complexes can be identified in plant cells with unprecedented resolution. This system allowed us to identify the composition of novel droplets, showing that they regulate RNA metabolism, regeneration, and vesicle trafficking (Solis-Miranda *et al.*, 2023, Mountourakis *et al.*, 2023, Liu *et al.*, 2023d, Liu *et al.*, 2023c, Liu *et al.*, 2023b, Liu *et al.*, 2023a, Hatzianestis *et al.*, 2023). Overall, our findings challenged the notion of discrete membrane organelles and unify processes seemingly distinct. We further introduced novel concepts in the field of hormonal regulation highlighting that although hormones converge on transcriptional repressors that can be degraded by the proteasome to initiate a response, the process of a less-explored proteolytic branch called 'limited proteolysis' seems to regulate hormonal signaling (Liu et al., 2023d). How the hormonal pathways are finely tuned at a cell-autonomous level is not known, while modes of regulation of timing in plant cells of regulation remain obscure. Our new results provide examples of modular protein networks with the ability to steer hormonal pathways.

Chen together with Andria, co-first authors of "A proxitome-RNA-capture approach reveals that processing bodies repress coregulated hub genes".

Other activities

- Chen Liu, the first postdoc of the lab secured an independent position as an Assistant Professor in Sun Yat-set, China
- The PI was awarded an ERC consolidator grant (2023 call)
- The PI is the director of the MS program "Green Biology" at the University of Crete
- We have an active role in the discussions about the usage and applications of CRISPR in plant biotechnology
- Organization of EMBO conference in Crete, 2021 bridging gaps between plant and animal cell death

Web page https://www.imbb.forth.gr/en/research-en/item/4119-panagiotis-n-moschou

Publications

Liu C, et al. (2023a) An actin remodeling role for Arabidopsis processing bodies revealed by their proximity interactome. **Embo J.** 42: e111885

Liu C, et al. (2023b) SEC14-like condensate phase transitions at plasma membranes regulate root growth in Arabidopsis. **PLoS Biol.** 21: e3002305.

Mountourakis F, et al. (2023) Concentrating and sequestering biomolecules in condensates: impact on plant biology. **J. Exp. Bot.** 74: 1303-1308

Panagiotis F. Sarris
Associate Professor - Collaborating Faculty Member

GROUP MEMBERS

Senior postdoctoral researchers:
Dr Vassiliki Michalopoulou
Dr Christos Christakis

PhD students:
Mrs Dimitra Tsakiri,
Mr Nikos Arapitsas,
Mr Savvas Paragkamian
co-supervision with Dr E. Pafilis–HCMR

Visiting students:
Alessandro Marchetti
PhD student from Prof. Marianna Lotti's Lab Università degli Studi di Milano-Bicocca - UNIMIB

MICROBIOLOGY, MOLECULAR HOST–MICROBE INTERACTIONS & PLANT IMMUNOBIOLOGY

Summary

In my group we are passionate about microbes (beneficial and pathogens) and the molecular mechanisms they use to colonize their hosts. Using functional patho-genomics and patho-proteomics, we investigate the microbial strategies for host's colonization (e.g. effector proteins, etc.), as well as the host's innate immunity system. We use plants as host model-systems to study Molecular Host-Microbe Interactions (MHMI). We are interested on the fundamental mechanisms regulating the "molecular dialogs" underlying MHMI for both the host and the microbe.

Current aims

To understand animal and plant colonization by microbes (beneficial and pathogenic), the most important challenge is to characterize the molecular mechanisms and the macromolecular structures that underlie host immunity, as well as microbial virulence.

Microbes (beneficial and pathogenic) use common strategies to colonize their animal and plant hosts. Virulence, for the majority of pathogens, largely depends on the delivering/translocation into eukaryotic host-cells of virulence proteins, known as "effectors". The exact role(s) and the subcellular targets of these virulence components remain an important open question in MHPI field, which has only partially been elucidated. Host intracellular NLR immune receptors are sensitive monitors that detect pathogens of both animal and plant cells. In both systems, NLR activation leads to a localized Programmed Cell Death (PCD). Recently we -and our collaborators- discovered that certain plant NLRs include additional domains to their canonical structure. We reported that these integrated protein-domains (IDs) act as "decoys" for pathogens. We found the origin of these IDs through the duplication of the effectors' original virulence targets.

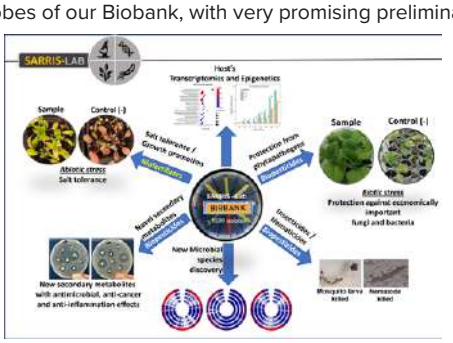
My group interests how plants resist disease using NLR-IDs, and in how resistance is overcome by pathogens.

What are the effectors' targets (in susceptible host-cell) and how their perception by NLR-IDs activates defence, is a crucial step in our in-depth understanding of host defence mechanisms, as well as, the microbial virulence.

Additionally, in my group, we investigate the role and potential use (as Biopesticides and Biofertilizers) of the cultivated microbiome from crop wild relatives (CWR) that live in extreme environments. We isolate new and known microbes that reveal interesting features regarding their ability to produce antimicrobials (antibacterial and antifungal compounds) against pathogens of clinical and agricultural interest, as well as other interesting features (e.g. anticancer and anti-inflammatory compounds).

Progress in 2022-2023

- We secured funding from three national grants. For two of them (with funding of 1mil and 195 thousand euros, respectively) my group was the coordinator.
- We published nine papers, some in high impact journals: a) two papers in The Plant Cell (one the corresponding group and one as a coauthors); b) two papers in The Plant Journal (as corresponding author); c) one paper in Plant Communications (as a coauthors).
- We created a Biobank of beneficial microbes that helped us to establish several interesting new collaborations in the IMBB (e.g. Prof. Vontas group; Prof. Papamatheakis; Prof. Moschou group; etc.), but also in other institutions, Universities, and the privet sector.
- We established the in-depth study of Cave-microbes from Greek caves and generated a network of European scientists on this field, for future European grant applications.
- We identified novel microbial species that produce secondary metabolites with anticancer and anti-inflammatory compounds and based on this finding we have already applied for a grant (in collaboration with Prof. Papamatheakis).
- We established a collaboration with students' exchange, with Prof. Marianna Lotti's Lab (Università degli Studi di Milano-Bicocca - UNIMIB) to investigate extremophilic enzymes production from the microbes of our Biobank, with very promising preliminary results.



Other activities

- Our research published in Cell in 2015 was highlighted as one of the most important discoveries in Biology for 2015 [*Science (2016), (Signaling, 9(409)*].
- We coordinate a project funded with ~1mil euro, to study the halophytic microbiomes and several bioactive plant components for their potential use as bioinoculants in a sustainable food production.
- Renewal of my Honorary Professorship at University of Exeter, 2020-25.
- We have trained a number of undergraduate and postgraduate students (Dept. of Biology, UoC).
- My PhD student Mr Nikos Arapitsas has been awarded the prize of the best PhD thesis and thesis presentation of 2023 from University of Crete.

Web page https://www.imbb.forth.gr/imbb-people/en/sarris-home

Publications

Kotsaridis K, et al. (2023) The functional and structural characterization of Xanthomonas campestris pv. campestris core effector XopP revealed a new kinase activity. **The Plant Journal** 116, 100–111 doi: 10.1111/tpj.16362

Michalopoulou VA, et al. (2022) The host exocyst complex is targeted by a conserved bacterial type-III effector that promotes virulence. **The Plant Cell** 34(9):3400-3424. doi: 10.1093/plcell/koac162

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Insects and Vector Borne Diseases

John Vontas

Professor - Collaborating Faculty Member

GROUP MEMBERS

Research Scientist / Staff Scientist:
Linda Grigoraki

Postdoctoral Researchers:
Kostas Mavridis
Staff Scientist
Vasileia Balabanidou
Maria Riga
Anastasia Kampouraki
Latifa Remadi
Panos Ioannidis
Kassiani Skouloudaki

Lab managers-Technicians:
Evangelia Morou
Dimitra Tsakireli

PhD students:
Sofia Balaska
Jason Charamis
Amalia Anthousi
Mengling Chen
Stefanos Mastis
Aikaterini Katsanou
Rafaela Panteleri
Kyriaki-Maria Papapostolou*
Giorgos Samantsidis*
Venetia Koidou*
Spyros Vlogianitis*
Mary Kefi*
Eva Katsavou*

* (PhDs awarded)

PEST AND VECTOR BIOLOGY & PEST CONTROL

Summary

Molecular entomology group

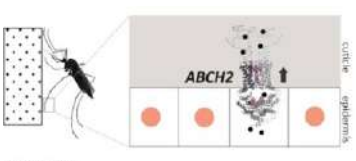
The Molecular Entomology group, led by Prof John Vontas, studies the mechanisms by which disease vectors and agricultural pests develop resistance to insecticides, as well as explores novel insecticide targets and biotechnology based approaches to increase the efficiency and sustainability of insect control interventions.

Current aims

We currently rely on insecticides to control insects that transmit deadly diseases and destroy our agricultural production. However, the evolution of insecticide resistance and the limited availability of highly selective and safe insecticides represent a major threat to human health and food security. Our research focusses on the molecular analysis of the mechanisms by which insects develop resistance to insecticides, aiming to develop means of managing and overcoming this resistance, such as molecular diagnostics and add-ons for improved insecticide formulations, respectively. We also aim the discovery of novel targets, for insecticide, biopesticide and biotechnology – based insect control solutions, using advanced multi-omic approaches and functional assays (such as cell based assays, CRISPR/Cas9).

Progress in 2022-2023

1. The lab elucidated several insecticide resistance mechanisms in mosquitoes and agricultural pests at the molecular level using a combination of in vitro and in vivo approaches. Genome editing was also applied in lepidoptera species and mosquitoes to functionally validating the role of genes and single nucleotide polymorphisms in insecticide resistance.
2. The ABCH2, an ATP-Binding Cassette transporter from the H family, was shown to regulate pyrethroid insecticide toxicity in the malaria transmitting An. *gambiae* mosquitoes, by pumping out of the mosquitoes' body the penetrated insecticide molecules. The transporter was found highly expressed in mosquitoes' legs, the first tissue that comes in contact with insecticide treated surfaces.
3. To address the limitations of existing diagnostic methods used in insect control programs novel multiplex TaqMan and ddPCR sample-to-answer assays were developed. These highly sensitive and practical diagnostic tools can reliably estimate the: a) species composition, b) presence and abundance of insecticide resistance markers and c) presence of human or plant pathogens, facilitating decision making in control interventions for agricultural pests, alien invasive species and disease vectors.
4. Holistic biotechnology based approaches using state-of the-art technologies were applied to enable the identification of potential insecticide targets in insect pests and mosquitoes, as well as elucidate the role of certain genes in insecticide pharmacokinetics. The model organism Drosophila melanogaster was used to investigate the role of ABC transporters in insecticide toxicity. Through RNAi screening, transgenic over-expression and immunolocalization the CG4562 and Mdr65 ABCs were implicated in insecticide transportation.



A transporter in mosquito legs acts like a pump, exporting insecticide out of the organism: Anopheles mosquitoes transmit malaria, exerting a tremendous public health burden, with the control heavily relying on insecticides. A new study published by IMBB researchers shows that a transporter, found in mosquito legs can remove the insecticide out of the organism acting like a pump. This mechanism could be targeted to restore insecticide toxicity.

Other activities

- In the frame of the EU Project ISIDORE/INFRA VEC2, we offered a large number of mosquito molecular genotyping "service" (Transnational Access, TNA) and provided support and training in researchers from >10 countries worldwide to advance their research in the field.
- In the frame of national and regionally programs, we provide scientific support and training for the implementation of control programs, against mosquitoes and major agricultural pests in Greece.
- ~15 undergraduate and master students received training and performed their thesis in the lab of Molecular Entomology

Web page
https://www.aua.gr/vontas/
https://www.imbb.forth.gr/en/research-en/biotechnology/item/2057-john-vontas

Publications

Kefi M, et al. (2023) ABCH2 transporter mediates deltamethrin uptake and toxicity in the malaria vector Anopheles coluzzii. **PLoS Pathog.** 19(8): e1011226. doi: 10.1371/journal.ppat.1011226

Denecke S, et al. (2022) Characterization of a novel pesticide transporter and P-glycoprotein orthologues in Drosophila melanogaster. **Proc. Biol. Sci.** 289: 20220625 doi: 10.1098/rspb.2022.0625

Nauen R, et al. (2022) The Role of Cytochrome P450s in Insect Toxicology and Resistance. **Annu. Rev. Entomol**. 67:105-124 doi: 10.1146/annurev-ento-070621-061328

Michail Kotsyfakis
Principal Researcher (B) –
Group establishment since April 2023

GROUP MEMBERS

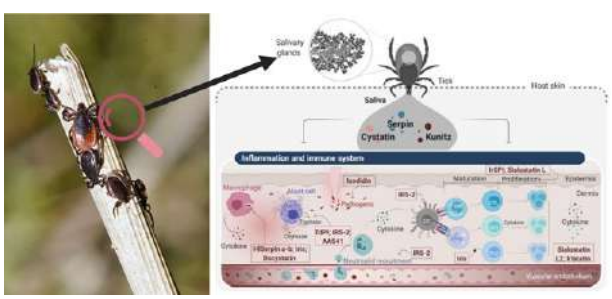
Special Research Assistant: (part time)
Renate Gessmann
PhD

PhD candidate:
Konstantinos Kostas
Vet/MSc

ARTHROPOD DISEASE VECTOR BIOLOGY

Summary

Ticks serve as model organisms to investigate critical aspects of Disease Vector Biology. The group aims to *strengthen surveillance* and *monitoring mechanisms*, with the goal of *enhancing preparedness* for scenarios where ticks could lead to public health issues in southern Europe. A significant portion of the group's efforts is dedicated to unravelling the molecular and biochemical intricacies inherent in the disease transmission lifecycle of arthropod vectors. This *comprehensive exploration includes a detailed investigation into the composition of tick salivary secretions and the elucidation of the intricate molecular processes* by which these secretions manipulate vertebrate hosts during tick feeding. Lastly, our research extends its f*ocus beyond fundamental understanding to explore practical applications of our findings in the health sector.* This involves a meticulous assessment of the potential of tick salivary molecules for drug development. Additionally, the group aims to pioneer the development of markers indicative of tick exposure, while actively contributing to the advancement of anti-tick vaccines. In essence, our research endeavours seamlessly integrate basic biological insights with tangible health-related applications.



We address the role of ticks at the ecosystem level and their impact on public health. Modern molecular approaches identify tick molecules that mediate tick vectorial capacity.

Current aims

Conceptually, two major research lines emerge from our work. The first focuses on the *epidemiological significance of ticks*, emphasizing the importance of establishing *surveillance and monitoring mechanisms for tick-borne diseases*. It underscores the need for preparedness in addressing disease emergence due to *expanding tick populations, partially due to the climatic change*, and advocates for proactive measures such as tick-exposure diagnostics, anti-tick vaccine development, education, and surveillance protocols to mitigate the impact of tick-borne diseases on public health.

The *second* line of our research centers on tick *saliva composition, its role in tick-host interactions*, and the potential applications of this knowledge in developing strategies to mitigate the impact of tick-borne diseases:

1. Exploration of tick saliva composition: We utilize transcriptomics and proteomics to analyse the composition of tick saliva and to understand the molecular mechanisms underlying tick hematophagy, pathogen transmission, and tick-host-pathogen interactions.
2. Investigation of the structure and function of tick protease inhibitors in tick saliva: Our focus is on the pluripotent and redundant pharmacological action of tick salivary protease inhibitors on the vertebrate host. We test tick salivary protease inhibitors as potential candidates for drug development in *in vivo animal models.*
3. Investigation of novel antigens for anti-tick vaccine and tick exposure diagnostic test development.
4. Role of nucleic acids in tick saliva: Our hypothesis is that tick *miRNAs regulate host genes and pathways* critical for the tick-host interaction and that tick *lncRNAs may act as "sponge" molecules to compete with host mRNAs for host miRNA binding.*

Progress since April 2023

On April 1st, 2023, our laboratory initiation at IMBB marked the commencement of a transformative journey. We successfully concluded a project centred on Ricistatin, a tick bioactive anti-proteolytic protein. Ricistatin, as a recombinant entity, is a potent inhibitor of host-derived cathepsins, showing a preference for host endopeptidases and limited impact on exopeptidase-driven proteolysis. The crystal structure of Ricistatin in complex with a host cathepsin illuminated, at the atomic level. the determinants of its restricted specificity. Additionally, Ricistatin demonstrated potent immunosuppressive and anti-inflammatory properties, highlighting its potential for immunotherapeutic applications.

During 2023, our collaborative efforts with laboratories in the USA and China resulted in two publications. The first focused on Guianensin, a blackfly salivary protease inhibitor and the second introduced a novel peptide, named Ranacin, showcasing its in vitro anticoagulant and antioxidant activities. Remarkably, Ranacin alleviated acute pancreatitis (AP) severity in mice, positioning it as a promising drug candidate for AP therapy, thus offering a multi-activity approach to improve pancreatic injury in severe AP cases.

Other activities

Michail Kotsyfakis was a *featured speaker* at the 12th General Meeting of the International Proteolysis Society, held from June 25 to 29, 2023, at the National University of Singapore. Kotsyfakis serves also as an *Associate editor* for journals like the International Journal of Molecular Sciences, Frontiers in Cellular and Infection Microbiology, BMC Genomics, and Life (Basel). He also teaches in the Graduate Program at the University of Crete (UOC), "Molecular Biology and Biomedicine'.

Web page https://www.imbb.forth.gr/en/research-en/item/6802-michail-kotsyfakis

Publications

Martins LA, et al. (2023) Protease-bound structure of Ricistatin provides insights into the mechanism of action of tick salivary cystatins in the vertebrate host. **Cell Mol. Life Sci.** 80(11):339

Valenzuela-Leon PC, et al. (2023) Guianensin, a Simulium guianense salivary protein, has broad anti-hemostatic and anti-inflammatory properties. **Front Immunol**. 14:1163367

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Inga Siden-Kiamos
Principal Researcher (B)-Emeritus since May 2019

GROUP MEMBERS

Postdoctoral researchers:
Chiara Currà
Elena Deligianni

PhD student:
Claude Preira

Special Research Assistants:
Lefteris Spanos
Renate Gessmann

Visiting students:
Sylvia Sorana
Diploma thesis (2022)
Elena Piselli
MSc student (2023)
Sofia diCastri
Diploma thesis (2023)
Monica Falcinelli
PhD student (2023)

PARASITOLOGY

Summary

Investigating the biology of the malaria parasite in the mosquito vector

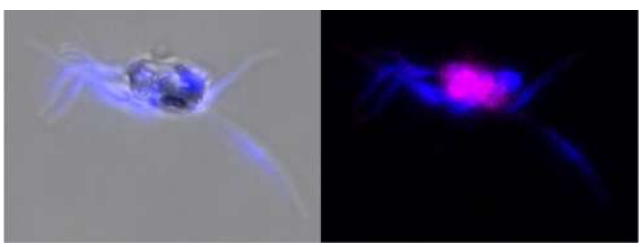
Malaria takes a heavy toll on human health in some of the poorest countries of the world, with about half a million deaths and 250-400 million new infections annually. Malaria is caused by the unicellular protozoan parasite *Plasmodium*, which is transmitted by mosquitoes. We investigate the biology of the parasite with emphasis on the mosquito stages with the goal to develop new strategies to control the disease.

Current aims

In the mosquito the parasite goes through a complex series of developments, that lead to the formation of the sporozoites, that are transmitted to a new host with the mosquito bite. The sporozoites develop in the oocyst in a syncytium, during about two weeks. We identified three proteins of the parasite which are necessary for completion of the oocyst stage and now aim to reveal their function. This knowledge can be used to develop inhibitors to block transmission of the parasite.
Malaria parasites encode two actin isoforms, with the major actin isoform being essential for cell motility. The second isoform, actin II, is required during the early mosquito stages early. Our goal is to elucidate the role of this actin isoform in the parasite life cycle.
We are testing compounds *in vitro* and *in vivo* for their direct inhibitory action against the mosquito stages of the parasite.
The olive fly, *Bactrocera oleae*, depends on a symbiotic bacterium for its survival. We investigate the bacterium as a target for olive fly control.

Progress in 2022-2023

1. To achieve a better knowledge of the proteins of the oocyst stage we carried out a proteomic analysis at three different time points during its development. Approximately 600 proteins were identified each with their temporal expression profile. This resource will be of use to future studies of the oocyst.
2. We determined the expression of the second actin isoform, revealing that the protein is expressed in the early sexual stages of the parasite. It is found associated with the nucleus in transient filament-like structures. Mutational analysis showed that post-translational modifications are essential for protein function. Our data reveal unique roles of actin II in these parasite stages, different from that of the major isoform actin I.
3. We tested the parasiticidal effect of 60 essential oils against the mosquito stages of *Plasmodium in vitro*. A subset of these showed strong inhibitory activity and a machine learning strategy identified compounds that can developed into parasiticidal agents.
4. We are using a combination of proteomic and transcriptomic analyses and imaging to investigate the interaction of the symbiont *Ca*. Erwinia dacicola with the olive fly. We have revealed how the physiology of the insect is harmonized with the bacterium to ensure the survival of both organisms.



Exflagellating male gametes. Actin II is present in the residual cell while the flagellar gametes are devoid of the protein. DNA is present mainly in the gametes. Right: brightfield and DNA (blue), left: actin II (pink) and DNA (blue)

Other activities

Our laboratory participates in Researcher's Night (funded by Marie Sklodowska Curie action) presenting our work on mosquitoes and malaria to the general public.
During 2022-2023 we received four visiting students from University of Camerino. Each carried out an independent research project.

Web page http://www.imbb.forth.gr/siden-kiamos

Publications

Deligianni E, et al. (2023) Screening of the activity of sixty essential oils against Plasmodium early mosquito stages in vitro and machine learning analysis reveals new putative inhibitors of malaria parasites. **Internation Journal for Parasitology Drugs and Drug Resistance** 23:87-93 doi.org/10.1016/j.ijpddr.2023.11.002

Lopez AJ, et al. (2023). Structure and function of Plasmodium actin II in the parasite mosquito stages. **PLoS Pathogens** 19(3): e1011174. doi: 10.1371/journal.ppat.1011174

Siden-Kiamos I, et al. (2022) Dynamic interactions between the symbiont Candidatus Erwinia dacicola and its olive fruit fly host Bactrocera oleae. **Insect Biochem. Mol. Biol**. 146:103793. doi: 10.1016/j.ibmb.2022.10379

Linda Grigoraki
Research Scientist / Staff Scientist

PEST AND VECTOR BIOLOGY AND PEST CONTROL

I joined the molecular entomology group of IMBB, as a staff scientist, in 2023. I participate and provide guidance, especially on functional genetics, in the various projects of the group focusing on the characterization of insecticide resistance in disease vectors and agricultural pests and the identification of novel methods for insect control.
In parallel I develop my own research projects, primarily on characterizing the genetics of mosquito insecticide resistance. Mosquitoes cause mortality and morbidity worldwide by transmitting diseases, like malaria, dengue, West Nile fever and Zika. The main way to prevent the outbreak of these diseases remains the use of insecticides. However, the strong selection pressure posed by the extensive use of insecticides has resulted in the emergence of highly resistant mosquito populations. If we want to efficiently manage this intensifying problem that threatens the efficiency of the few available insecticides for mosquito control, we need to understand its genetic basis. I use functional genetics (genome editing and transgenesis) to determine the role of genes and their mutations in conferring resistance to insecticides, as well as to measure the effect size of each mechanisms and study the combined effect of different mechanisms that often co-exist in resistant populations. I am also interested in investigating the impact of insecticide resistance on the efficiency of volatile insecticides, a unique category of insecticides that disrupts the host seeking ability of mosquitoes. My research projects involve collaborations with researchers from the Liverpool School of Tropical Medicine and the Benaki Institute. In 2023 I obtained a grant from the Hellenic Foundation for Research and Innovation.

Web page https://www.imbb.forth.gr/grigoraki

Pantelis Topalis
Senior Staff Scientist – Bioinformatics

GENOMICS & DATABASES

My main interests are
a) to analyze gene expression and regulation from high throughput sequencing datasets and
b) to assemble, annotate and compare newly sequenced genomes whith a special focus on insects and human pathogenes.
Other interests include the development of databases and bioinformatics tools using ontologies and other sematics approaches to promote interoperability between different but related datasets.
In parallel, I assist IMBB's research groups to analyze their data using bioinformatics tools; participate in research proposals and collaborate with other research team providing customized bioinformatic services that fit the specific needs of a project and; provide practical training to methods, tools and services to IMBB members and in general taking advantage of all modern tools of e-learning. The long term goal is also to develop and setup a virtual research environment where the users could use predefined workflows (or design their own) to analyze their data.
In the last period, in the frame of the EU Infrastructure program INFRAVEC2, I analysed insect genomic data related to Sterile Insect Technique (SIT) applications against mosquito vectors. Our results suggest that random mutations induced by a sub-sterilizing dose of gamma ray in Ae. albopictus male pupae and transmitted to the male progeny of the irradiated mosquitoes do not affect biological processes potentially harmful, from a public-health point of view.

Web page http://www.imbb.forth.gr/bsg

George Dimopoulos (Johns Hopkins Malaria Research Institute)

Adjunct Researcher, ERA Chair IMBB-FORTH

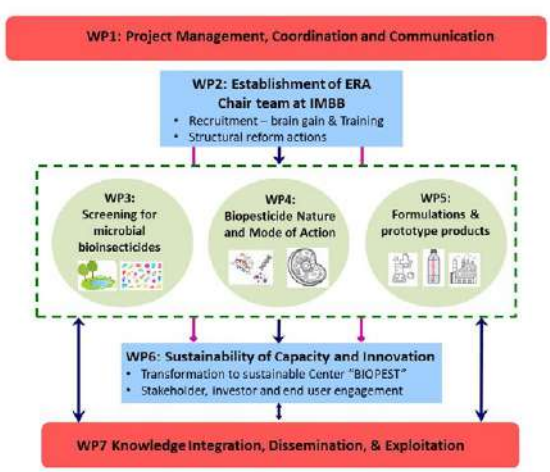
GROUP MEMBERS

Dr Martyn Wood,
Dr Joel da Cruz Couceiro
Dr Juan Silva
Andronikos Papadopoulos
PhD student
Stefanos Mastis
PhD student
Maria Mazavli
final year student UoC
Katerina Kanelli
final year student UoC
Iliana Sidira
final year student UoC
Kostas Mavridis
Inga Siden-Kiamos

VECTOR BIOLOGY-BIOTECHNOLOGY

Prof George Dimopoulos (Johns Hopkins University) joined IMBB in 2022 as its first ERA-Chair to strengthen Vector Biology/Green Biotechnology division. Dr. Dimopoulos' research aims at understanding the biology of mosquito – pathogen interactions to develop novel intervention strategies. His current research program broadly focuses on the innate immune systems and microbiomes of the mosquito disease vectors Anopheles and Aedes, and how these can be harnessed to attenuate transmission of malaria and arboviral diseases. Another area of translational research is the development of cost-effective and eco-friendly microbial biopesticides for mosquito control.

The ERA Chair Project of Prof. George Dimopoulos has established the MicroBioPest research team at IMBB, aiming to develop environmentally safe microbial biopesticides, for the control of mosquito vectors of human diseases and agricultural pest insects (Figure 1). The research plan includes innovative components and state of the art methodologies for the identification of insecticidal microorganisms, elucidation of their mode of action and insecticidal active molecules, eventually leading to prototype product development.



First year progress

An international team was established at IMBB comprising 3 postdoctoral fellows, 2 PhD graduate students and 3 undergraduate trainees, and a senior collaborative researcher and an administrative analyst. Disparate habitats in Crete were surveyed extensively to establish a library of about 1700 bacterial and fungal isolates many of which were screened for larvicidal activity against *Culex pipiens*. Results demonstrate promising potential of several of bacterial and fungal isolates, with over 10 unique isolates exhibiting significant potential for the development of future biopesticides. Heat inactivation, sonication and solvent extract data provided further insights, with non-polar extractions providing the majority of lethality. Several isolates possess highly heat-stable insecticidal activities, pointing at likely stable metabolites with long shelf-life. The molecular characterization of the bacteria isolates, the identification of the active ingredients and their mode of action are currently being pursued. Similarly, several discovered entomopathogenic fungi are also being characterized for their suitability as future insect pest control agents. In sum: the EA Chair Team has identified numerous microbial isolates showing promising biopesticidal activities, with different degrees of potency. Ongoing studies are focusing on the spectrum of activity and other characteristics of these isolates to evaluate their suitability for development as biopesticides.

Web page
http://www.dimopoulosgroup.org/
https://www.jhsph.edu/faculty/directory/profile/1215/george-dimopoulos

Publications

Belavilas-Trovas A, et al. (2023) Long non-coding RNAs regulate Aedes aegypti vector competence for Zika virus and reproduction. **PLoS Pathog.** 19(6): e1011440

Engdahl CS, et al. (2023) Chromobacterium Biopesticide Exposure Does Not Select for Resistance in Aedes Mosquitoes. **mBio.** 14(2): e0048023.

Engdahl CS, et al. (2022) Discovery of novel natural products for mosquito control. **Parasit Vectors** 15(1):481

Affiliated and Adjunct Faculty

Triantafylos Chavakis
Technical Univ. Dresden
INNATE IMMUNITY AND IMMUNOMETABOLISM

George Diallinas
Universiy of Athens
REGULATION OF CELLULAR EXPRESSION, STRUCTURE, FUNCTION AND EVOLUTION OF TRANSPORTERS

Alex Dömling
University of Groningen
CHEMICAL BIOLOGY

Paul Lasko
McGill University
TRANSLATIONAL GENE REGULATION

Jean-Paul Latgé
Institute Pasteur
INFECTIONS AND IMMUNITY

Michail Lionakis
NIAID/NIH
CLINICAL IMMUNOLOGY AND MICROBIOLOGY

Ioannis Mitroulis
Technical Univ. Dresden
INNATE IMMUNITY AND HEMATOPOIESIS

Facilities

Iannis Talianidis
Scientific Director

Theodoros Kosteas
Co-Head Of Core Facility

FACILITY MEMBERS

Veterinarians:
Costas Kourouniotis
Eleni Moltsanidou
Debbie Tsoukatou
part time

Animal Technologist:
Hara Roumpaki

Animal Technicians:
Eleni Ntagiasi
Androniki Vardoulaki
Stella Chalkiadaki
Sonia Kantali
Konstantina Sarri
Eirini Charitaki

Support Technician:
Ektoras Xenakis

ANIMAL (MOUSE) HOUSE AND GENE TARGETING FACILITY

Summary

The use of mice for scientific and research purposes is a practice that has substantially contributed to the promotion of biomedical science. The Animal (mouse) / Genome Editing Core Facility at the IMBB – FORTH have significant experience in animal welfare, the production of transgenic / genetically modified mice as well as in housing, supplying and breeding them for basic and translational research. Our unit provides high-standard services towards 26 biomedical research groups, executed by a team of 13 highly skilled and experienced personnel in a modern up-to-date facility. Our infrastructure consists an independent mouse facility of 1,500m^2, the largest in Greece, consisting of 4 units (SPF, experimental, behavioral & quarantine) and one of the two available transgenic/genome editing facilities nationwide. Our facility operates in accordance with the National (Presidential Decree 56/30.04.2013), the European Directive (2010/63/EU) and in accordance to the Guidelines issued of the Federation of European Laboratory Animal Science Associations (FELASA). It operates under licenses issued from the Veterinary Service Office of the Prefecture of Crete: EL91-BIObr-01 and EL91-BIOexp-02, for the establishment & breeding and for the use of mice for scientific purposes.

Current aims

Our facility is a partner in the EU funded INFRAFRONTIER GR/ Phenotypos program and a member in the EU-LIFE network of Core Facilities. We have the available infrastructure, experience and have started to implement the latest CRISPR/Cas9 methodologies for the rapid generation of conditional knock-out mouse models and the cryopreservation and archiving of our mouse lines. These skills and qualities are central towards achieving the best performance and competitiveness for our institute and our collaborators.

These methodologies will have an important impact on our facility and will allow us to further:

1. Accelerate our services in a cost-effective time frame required for the generation of new mouse models.
2. Help reduce the number of mice being utilized in the procedure.
3. Provide available funding which will be directed towards our facility/ institute rather than to commercial suppliers.
4. Enhance, improve and promote the competitiveness and collaboration of the services offered from our core mouse/genome editing facility to our institute and the University of Crete.
5. Cryo-preserve and deposit custom-engineered conditional knockout animal models to the European Mouse Mutant Archive (EMMA).

Progress in 2022-2023

Through available funding provided by the INFRAFRONTIER, EU and the IMBB, our main task was to upgrade, introduce and provide new services towards our research groups by: i) recruiting new personnel ii) upgrading our SPF facility iii) installing an air shower and cage/ bottle washer iv)expanding our neurobehavioral laborotories and v) upgrading our transgenic/genome editing through the purchase of new scientific instruments such as: a) an Eppendorf micro-manipulator unit b) a NEPA21 electroporator and c) a Zeiss inverted microscope.

Selected impact activities

Members from our facility participated in various meetings, courses and received training fellowships:

- Members from our facility participated as instructors at the annual 8th and 9th FELASA accredited Course on the Care & Use of Laboratory Animals.
- T.K. visited the Genome Editing Facility of Tokai University, Japan. Funding provided from the IMBB and an EMBO Core Facility Fellowship.
- Co-organization of the EU Life TechWatch series
- EU Life Core Facilities publication: Acknowledging and citing core facilities. EMBO Rep. 2022 Sep; 23(9).

i) Genome Editing Lab ii) Purchase of cage/bottle washer iii) Installation of an air shower unit

Links

http://www.imbb.forth.gr/en/facilities-en/cells-animals/item/2-gene-targeting-facility-gtf
http://www.imbb.forth.gr/en/facilities-en/cells-animals/item/1-animal-house
https://www.imbb.forth.gr/imbb-people/en/animal-house
https://www.infrafrontier.gr/phenotypos
http://www.felasa.eu/working-groups/guidelines/felasa-guidelines-and-recommendations/
https://eu-life.eu/research-excellence/working-groups-task-forces/core-facilities
https://www.imbb.forth.gr/imbb-people/en/animal-house-publications

Matthieu Lavigne
Head of facility

FACILITY MEMBERS

Research assistants:
Eirini Stratidaki
Niki Gounalaki
Data management and analysis:
Emmanouil Dialinas

GENOMICS FACILITY

Summary

For the past 20 years, Next Generation Sequencing (NGS) technologies have been revolutionizing genetic and genomic research, providing unpreceded depth and detail in transcription regulation, RNA synthesis and chromatin functions in health and disease. Numerous NGS applications are now routinely used in biomedical research. The IMBB Genomics Facility offers experimental consulting, quality control, library preparation, sequencing and analyses services to IMBB researchers and external users.

We assist scientists to advance their research by generating high quality workflows that maximise the quality of sequencing data from difficult/precious samples. By optimizing techniques and by working close with the facility users, we are able to offer a personalized experimental design, propose the best suited experimental approach, tailored to the projects needs and available resources.

A key advantage of our service is also that we offer basic bioinformatics analysis and data interpretation without charge to guarantee access to the technology and maximization of the biological insights to non-experienced users.

Capabilities

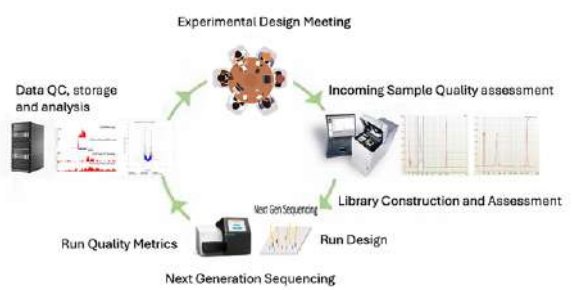
The facility uses the Illumina NextSeq 500 instrument routinely and partners with the facility of Medical School of the University of Crete to acces to larger loads of sequencing on the recently purchased NextSeq 2000. Sequencing for specialized applications such as metagenomics is performed on Illumina MiSeq at HCMR, Heraklion. We also work with the ANCIENT DNA AND POPULATION GENOMICS facility to produce long read sequencing experiments on Oxford Nanopore Technology MinION platform. The Genomics facility has several years' experience in the following services:

1. RNA-sequencing
2. DNA-seq and ChIP-sequencing
3. ATAC-seq
4. 16S rRNA sequencing for micro- biota analysis.
5. Whole Exome and gene panels Sequencing

The facility is also equipped with instruments for library preparation and QC (Agilent Bioanalyser, Thermo Scientific Qubit platform, qPCR...)

Progress in 2022-2023

- Optimized ratio quality/cost for the 3'-quant-seq RNA-seq protocol that enables low input/quality RNA samples to be processed and can generate lists of Differentially expressed genes (DEGs) with similar quality to more expensive and tedious protocols for full length RNAseq.
- Upgrade performances of the Genomics Server (32-core, 128GB RAM, 20TB storage) that is essential for raw data storing and implementation of pipelines for sequencing/data quality assessment/delivery of basic analyses to the users: New High Performance Cluster (HPC) funded by IMBB to allow bioinformaticians of the new Horizontal inter-bioinformatics unit (HIBU) to work on NGS datasets generated in house or downloaded from databases.
- Constant increase in users and samples numbers processed by the facility.
- Development of workflow and strategies to be able to bring single-cell technologies to IMBB users in the near future.
- Developed efficient protocol to accommodate users needs to precious and difficult to acquire samples with extremely low input RNA-seq (from few thousands of cells isolated by FACS)
- Minimized sequencing costs for users (IMBB researchers benefit from lower rates thanks to our policy to no charge of technician cost or overheads), making NGS for affordable but at the same time providing high quality sequencing data.



Workflow at IMBB Genomics Facility: from the scientist and back

Other activities

Participated in the annual Researchers Night and Science Festival, in the ITE-FORTH retreat and in FORTH School visits presenting the available technologies and highlighting the contribution of NGS applications in advancing scientific knowledge to the broader public.

Web page
https://www.imbb.forth.gr/imbb-people/en/genomics-facility-home
http://www.imbb.forth.gr/en/facilities-en/molecular-biology-services/item/17-genomics-facility

Publications

Tselika M, et al. (2023) Nicotiana benthamiana plants has a minor yet detectable effect on CG methylation. **Front Plant Sci.** 14:1258023. doi: 10.3389/fpls.2023.1258023

Galanopoulou O, et al. (2023) Endonucleosis mediates internalization of cytoplasm into the nucleus in senescent cells. **bioRxiv** doi. org/10.1101/2023.11.12.566736

Christos Delidakis
Head of facility

Elena Deligianni
Head of facility

FACILITY MEMBERS

Postdoctoral scientist:
Margarita Stapountzi
Lab Technician:
Alexandros Babaratsas

ADVANCED MICROSCOPY

CONFOCAL MICROSCOPY

Summary

Analysis of complex biological systems relies greatly on high quality optical imaging of both fixed and live specimens. Laser scanning fluorescence confocal microscopy is the platform of choice for such observation and is widely used by most IMBB groups for a great variety of assays.

Capabilities

Our main workstation is an inverted Leica SP8 scanning confocal microscope. An older Biorad µRadiance 2000 fitted to an upright Zeiss microscope is rarely used, but still serves as a regular widefield fluorescence microscope. The SP8 is equipped with two scanners, a regular one and a fast resonant scanner, and allows for a selection among eight different laser wavelengths (405-633 nm) for excitation of fluorophores throughout the light spectrum. The microscope is connected to an environmental chamber with controllable temperature and CO2 for live cell/tissue imaging. Additional modules, such as FRAP and Live Data Mode, can be used for complex experiments and subsequent analysis.
Individual users are trained by the main facility scientist, Margarita Stapountzi. They are allowed to use the platforms only after completing at least 15 hours of theoretical and hands-on training. At the end of 2023 we had 120 accredited users from 39 research groups. A large variety of fixed and live samples are imaged in our facility, including cells dissected tissues or whole organisms.

Progress in 2022-2023

We installed a "Navigator" module to allow interactive automated sample imaging. Usage has been steadily increasing and we are making plans for addition of a second platform, especially since the present one will soon reach a decade of age.

Other activities

Examples of recent activities supported by the facility are:

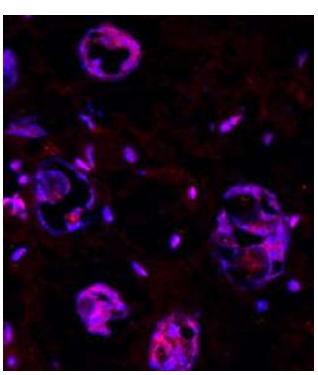
- Studying nuclear lamin dynamics
- Imaging chromosomal territories by Chromosome Painting
- Imaging of pathogenic and symbiotic bacteria effectors' subcellular localization, to discover novel host-cell targets.
- Immuno-RNA-DNA FISH experiments for the study of 3D nuclear organization of primary murine thymocytes
- Brain imaging of murine animal models that age in an accelerated manner
- Live imaging of Drosophila neural tumours and their interaction with macrophages
- Live cell imaging of Arabidopsis root epidermal meristematic cells – FRET-SE

THE HIGH CONTENT SCREENING MICROSCOPY UNIT

Summary

The HCSM provides biomaging services including image acquisition and image analysis as requested for research projects within IMBB/FORTH and IMBB affiliated members. The facility is equipped with an Operetta High Content Screening system (Perkin Elmer). A typical HCS assay is capable of generating automatically thousands of images, followed by automated analysis. Using assay-specific pipelines we can image the samples, analyse images and present findings. Imaging is available for 3D, fixed and live samples. Analysis is based on the cell morphology as it assessed by fluorescence markers. HCSM is the ideal tool for drug screening and discovery, as well as observing morphological changes during assays. Typical applications where HCSM can be incorporated include Measurement of Neurite outgrowth, Cell migration, Cell growth, proliferation and differentiation, Cell death, Apoptosis, Autophagy, Assessment/Monitoring of the cell cycle and DNA damage, Cell stress, Cell differentiation, Cell metabolism, Ca+2 signaling and Cell tracking.

The facility is certified under ISO standard protocol for best practice for the years 2022, 2023, 2024. (Dr. Elena Deligianni has more than 10 years' experience in HCS applications).



Hepatocyte staining to access morphological and biochemical changes in hepatocytes

Web page

http://www.imbb.forth.gr/en/facilities-en/imaging/item/14-advanced-microscopy-unit
http://www.imbb.forth.gr/en/facilities-en/imaging/item/813-advanced-multiphoton-confocal-microscopy
http://www.imbb.forth.gr/en/facilities-en/imaging/item/3295-high-content-screening-microscopy-unit

Publications

The confocal Facility is acknowledged in a large number of the Institute's publications, too numerous to list.

Tselika M, et al. (2023) Nicotiana benthamiana plants has a minor yet detectable effect on CG methylation. **Front Plant Sci.** 14:1258023. doi: 10.3389/fpls.2023.1258023

Galanopoulou O, et al. (2023) Endonucleosis mediates internalization of cytoplasm into the nucleus in senescent cells. **bioRxiv** doi. org/10.1101/2023.11.12.566736

Constantine A. Stratakis
Professor – RESEARCHER A'

GROUP MEMBERS

Principle Staff Scientist:
Dr. Emmanouela Linardaki

Post-Doctoral Researchers:
Evmorfia Tzagkaraki
Elena Vorgia
Dionysia Petratou
Rodanthi Lyraki

Research Assistants (MSc):
Polymnia Gkoumplia
Bioinformatics

DIAGNOSTIC GENETICS AND PRECISION MEDICINE UNIT

Summary

Precision Medicine (PM) is a new approach in the treatment and prevention of disease that takes into account the differences between individuals in terms of their genetic characteristics, environment and lifestyle. PM is fundamentally changing the way treatments are developed. The targeted, personalized approach to healthcare is having a broad impact, from genomics to medical devices, and as a result is creating new business models for companies across the sector. At the same time, it provides the background for studies that investigate the interaction of genetic factors, environmental factors and lifestyle in our body and the effect of these on the promotion of health or the development of diseases.

The Diagnostic Genetics and Precision Medicine (DIGENIA) Unit of FORTH-IMBB is a state of the art, ISO-15189 accredited, molecular biology and genetics laboratory, with a focus on medically related research, technologies and analyses and, in particular, in the rapidly growing field of personalized genomic analysis. Our mission is to develop and make accessible to the entire Greek population and internationally cutting edge genetic and genomic diagnostic technologies, to provide advanced and reliable health services based on the new, emerging, preventive and personalized medical practice, and at the same time to promote research in all branches of bioinformatics and -omics applications, ensuring continuous development at the level of technology and know-how and specialization of our human resources. Our goal is to provide innovative and high-quality services and to make a substantial contribution to research and development in the field of human health.

Current aims

1. Development and provision to the general public, to clinicians (and other professionals of the biomedical community) accessible, reliable, advanced and specialized technologies, applications, products, as well as services, based on the most modern and high-tech methodologies, and strict quality assurance rules with emphasis on the areas: 1) Genomic Analysis and Diagnostics 2) Personalized medicine and precision medicine, 3) Pharmacogenomics 4) Molecular Biology and Genetics, 5) Biomedicine, 6) Medical Genetic counseling, 7) other biomedical fields.
2. Research into the genetic causes associated with the pathogenesis of genetic and other diseases with the aim of developing new genetic markers, diagnostic and prognostic genetic approaches and analyses.
3. The development of advanced computational methods, algorithms and bioinformatics platforms for the management, processing, annotation, evaluation, interpretation and presentation of large-scale data generated by genomic, proteomic, metabolomic, and other –omics analyses and clinical studies data.

Progress in 2022-2023

In the context of our research interests, DIGENIA has coordinated or participated in all National Networks of Precision Medicine in Greece:

- Hellenic Precision Medicine Network in Oncology - EDIAO (oncopmnet.gr): analyzed over 700 clinical samples using custom designed targeted NGS panels for solid tumor and hematologic malignancies, for the identification of clinically actionable gene mutations, relevant to treatment and prognosis
- Greek National Network of Precision Medicine in Cardiology and the Prevention of Sudden Death in the Young - EDIAK (icardiacnet.gr): analyzed over 170 clinical samples of patients and first and second degree relatives using targeted NGS panel for hereditary cardiac conditions and Sanger sequencing
- Hellenic Precision Medicine Network for Neurodegenerative Diseases - EDIAN (neuropmnet.gr), analyzed over 100 clinical samples by Whole Exome Sequencing analysis for identifying predisposing or disease causing mutations in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, chorea etc.

During 2022-2023, the Hellenic Network for Precision Medicine in Molecular Oncology - EDIMO (www.edimo.gr) was established as a National collaborative research consortium. DIGENIA received a grant through the NextGenEU and the General Secretariat for Research and Innovation of the Hellenic Ministry of Development to coordinate EDIMO as the leading laboratory. Thus, at DIGENIA and EDIMO, along with 7 other centers and laboratories around Greece, we support research on new genetic and other markers to identify tumor indices that can be used for the diagnosis, therapy and follow-up of patients with neoplasms.

Diagnostic Genetics and Precision Medicine Unit, Hellenic Precision Medicine Network EDIMO.

National Networks of Precision Medicine DIGENIA has participated and/or coordinated.

Other activities

- DIGENIA is part of the smartHEALTH European Digital Innovation Hub
- DIGENIA is part of the Health Hub European Digital Innovation Hub

Web page
www.digenia.gr
www.edimo.gr

Publications

Tsaknakis G, et al. (2021) Incidence and Prognosis of Clonal Hematopoiesis in patients with Chronic Idiopathic Neutropenia. **Blood** 138(14):1249-1257

Tzagkaraki E, et al. (2022) Inherited Cardiac Disorders: Identification of known and novel disease-associated genetic variants in the Cretan population. **1ο Πανελλήνιο Υβριδικό Συνέδριο Ιατρικής Γενετικής** 14-16 Οκτωβρίου

Ταβερναράκης Ν, et al. (2023) Identification of a novel variant in the MYBPC3 gene associated with hypertrophic cardiomyopathy. **44° Πανελλήνιο Καρδιολογικό Συνέδριο**, 12-14 Οκτωβρίου

Giorgos Gouridis
Head Of Facility

Nikos Kountourakis
Facility Manager

Charalampos Pozidis
Facility Manager

FACILITY MEMBERS

Facility Data Scientist:
Kostas Tsolis
Facility Technician:
Sofia Kaforou

PROTEOMICS FACILITY (PROFI) / PROTEIN PURIFICATION-CHARACTERIZATION UNITS

Summary

Proteomics facility at IMBB (ProFI) is equipped with state-of-the-art mass spectrometry-based proteomics and bioinformatics tools, applying various approaches and developing new methodologies, particularly for the identification and characterization of proteins. ProFI's highly trained and experienced staff provide excellent research and work as service facility to researchers within IMBB, but also to external academic and industrial laboratories.

Capabilities

A) A high-resolution tandem mass spectrometer (LTQ-Orbitrap XL with ETD) coupled to an Easy nLC (nano Liquid Chromatography; Thermo Scientific) is situated within the facility.

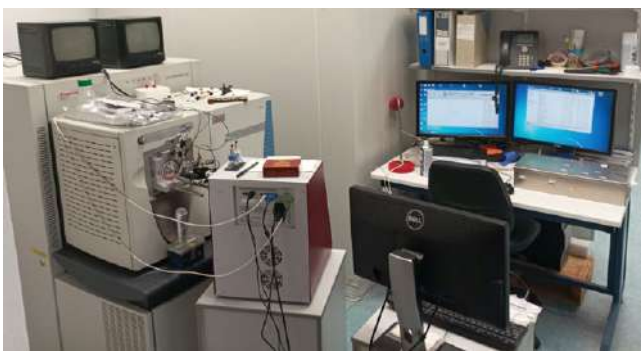
B) Application of established and development of new bottom-up and top-down shotgun proteomic and analyses, including:
- Biomolecule mass determination by mass spectrometry
- Protein identification and quantitation for many biological systems and questions
- Study of protein post-translational modifications and interactions
- Help and advice on any aspect of the application of proteomics and bioinformatics to the exploration of biological problems.

Progress in 2022-2023

- Completion of more than 30 submitted projects:
- IMBB and IESL-users
- Dpt. Chemistry - University of Crete
- External users: Duth University, Dublin University, Cyprus University
- Commercial users completed: Bayer

Other activities

EPIC-Xs annual meeting at IMBB, Cutting-edge Mass Spectrometry technologies



LTQ Orbitrap XL at ProFI

The Unit also includes the following support facilities:

- **Macromolecular Analysis Unit**
http://www.imbb.forth.gr/en/facilities-en/macromolecules/item/9-macromolecular-analysis

- **Biophysical Analysis Unit**
http://www.imbb.forth.gr/en/facilities-en/macromolecules/item/10-biophysical-analysis-biosensors

- **Crystallography Unit** (run by Petratos/Renata)
http://www.imbb.forth.gr/en/facilities-en/macromolecules/item/8-protein-crystallography

PROTEIN PURIFICATION FACILITY

Protein Purification and Characterization Core Facility

The facility purifies proteins from E.coli, insect, mammalian cells and sera using a variety of chromatographic methods, from milligram up to grams scale, using a large variety of chromatographic techniques. Furthermore, we also can provide biophysical characterization of purified proteins such as, molecular mass determination or molecular weight, molar mass distributions of heterogeneous samples, accurate aggregation and oligomeric states of proteins, stoichiometry of tightly bond protein heterocomplexes, determination of mass-averaged root mean square radius etc. We also develop or evaluate new techniques and advanced protocols for protein purification and there is significant focus on developing time-saving solutions for these activities.

Progress in 2022-2023

During these two years the facility continued the well-established collaboration with many of the institute research groups on a range of projects involving either protein purifications or biophysical characterization of purified proteins.

Web page
http://www.imbb.forth.gr/imbb-people/index.php/en/welcome
https://www.imbb.forth.gr/imbb-people/en/protein-purification-facility-hom

Publications

Kotsaridis K, et al. (2023) The functional and structural characterization of Xanthomonas campestris pv. campestris core effector XopP revealed a new kinase activity. **Plant J. Oct**;116(1):100-111. doi: 10.1111/tpj.16362

Zelenka T, et al. (2023) A novel SATB1 protein isoform with different biophysical properties. **Front. Cell Dev. Biol.** 11:1242481 doi. org/10.3389/fcell.2023.1242481

Christos Delidakis
Head of facility

FACILITY MEMBERS

Research assistants:
Ioannis Livadaras
Head Technician, microinjection specialist
Alexandros Babaratsas
Drosophila stock maintenance
Lefteris Spanos
mosquito rearing

Fly kitchen personnel:
Melina Karyotaki
Georgia Nistikaki

FLY ROOM INSECTARIUM

Summary

The Insect facility provides the infrastructure and the technical support for rearing and experimentation on different insects used in programs of basic and applied research. It is a housing facility for a number of insects: fruitflies, medfly, olivefly, cotton bollworm, and other agricultural pests as well as insects of medical importance (mosquitoes). Furthermore, the facility equipment supports genetic experiments performed by the members of several groups as well as the production genetically manipulated lines for the majority of the above insects. Four research groups are associated with the facility and use the premises in an everyday basis for fly/insect work. Occasionally researchers from other parts of Greece or abroad are hosted and their research is supported by the facility through collaborative research programs.

Capabilities

- The main Insect rearing space of the facility is made up of three walk-in incubators with controlled humidity, temperature and light-dark cycle which surround the central Fly-room space. An additional walk-in incubator is used for lepidoptera rearing and two isolated spaces are dedicated to mosquitoes' rearing and handling.
- The central Fly-room space is a large lab with 5 work stations equipped with stereo-microscopes, light sources and anesthetization stages connected with a centralized CO2-delivery system. A dark chamber for fluorescence stereo-microscopy completes the setup.
- Highly experienced technicians are responsible for the maintenance of insect stocks and provide technical assistance to researchers and training of the newcomers.
- The facility also includes a separate lab space dedicated to insect embryo microinjections which is equipped with a state-of-the-art system for embryo injections. Ioannis Livadaras, our microinjection technician, is very experienced not only in routine Drosophila melanogaster transgenesis but also in producing transgenic and CRISPR lines for other insects (i.e medfly, olivefly, flour beetles, cotton bollworm). The microinjection facility is also used for other purposes, such as transplanting tumours and inoculating pathogens into insect hosts.

Progress in 2022-2023

A new suite for mosquito rearing with climate controlled culture room was set up.

Projects that have made extensive use of the facility:

- A pipeline for generating neural stem cell tumours in *Drosophila* larvae and transplanting / propagating them in adult hosts was developed earlier and is currently improved and heavily used for understanding tissue tumorigenesis.
- Several CRISPR projects have been carried out in *Drosophila* and non-model insect pests, such as in olive fruit fly, *Tetranychus urticae* and *Helicoverpa armifera*, aiming to characterize insecticide resistance mechanisms and/or validate the discovery of novel insecticide targets for pest control.
- Development of biotechnology –based innovative approaches for olive fruit fly control, via targeting its symbionts (dysbiosis)
- *Drosophila* models of infectious diseases have been established in order to genetically dissect evolutionarily conserved pathways in hemocytes immunity (macrophage-like cells)

Other activities

- The facility was represented in the Researchers Night and Science Festival annual events held at FORTH in 2022. We presented aspects of the biology of the insects reared in the facility to students of primary and secondary schools as well as to the broader public who visited our stand, highlighting the impact of the related research programs on medical and agricultural issues.
- The facility hosted visits and tours from high school students as part of school programs to promote careers in science.

Web page www.imbb.forth.gr/imbb-people/en/flyroom-insectarium-home

Publications

Voutyraki C, et al. (2023). Growth deregulation and interaction with host hemocytes contribute to tumor progression in a Drosophila brain tumor model. **Proc. Natl. Acad. Sci.** U S A. 120(33): e2221601120 doi: 10.1073/pnas.2221601120

Lopez AJ, (2023) Structure and function of Plasmodium actin II in the parasite mosquito stages. **PLoS Pathogens** 6,19(3): e1011174. doi: 10.1371/journal.ppat.1011174

Theodorou V, et al. (2022) ASC proneural transcription factors mediate the timely initiation of the neural program during neuroectodermal to neuroblast transition ensuring progeny fidelity. **BMC Biol**. 20:107 doi: 10.1186/s12915-022-01300-8

Siden-Kiamos I, et al. (2022) Dynamic interactions between the symbiont Candidatus Erwinia dacicola and its olive fruit fly host Bactrocera oleae. **Insect Biochem. Mol. Biol.** 146:103793. doi: 10.1016/j.ibmb.2022.103793

Androniki Kretsovali
Head Of Facility

George Vrentzos
Head Of Facility

CELL CULTURE FACILITY

Summary

Since 1985, IMBB maintains a self-contained Cell Culture Facility that houses all equipment needed for the growth, maintenance, and analysis of animal cells. The facility provides basic support to investigators: preparation, filtration and testing of numerous cell culture media and is a source of culture supplies and sterile reagents. The facility provides technical support for a) growing a range of different cell lines and hybridomas including mammalian and insect cell lines as well as primary cells b)large scale cell cultures c)transfection of cells and expansion of different clones. The main facility is located on the 1 st floor (Room A208) of the IMBB building and has three separate rooms equipped with HEPA filtered air flow and UV lamps. A second part of the facility is housed in the basement of the Institute and accommodates insect cell cultures, the parasite transgenesis laboratory and tissue engineering activities. The cell culture facility complies with all the EU regulations regarding biohazard material handling and disposal.

Equipment

The cell culture facility contains:

- Ten laminar flow hoods, biosafety level II for the sterile handling of cells,
- Ten CO_2, 37° C incubators for growing mammalian cells
- Five 25° C incubators for insect cell lines
- Four refrigerated centrifuges
- Microscopes:
    1. OLYMPUS IX-70 Inverted fluorescence microscope + HAMAMATSU CCD Camera
    2. Leica DM-IL Inverted fluorescence microscope + Leica DFC-310FX Camera
    3. ZEISS PrimoVent Inverted microscope + ZEISS Axio Cam Erc5s
    4. Euromex FE 2955 Inverted microscope
    5. Nikon ECLIPSE TE 2000-U Inverted fluorescence microscope
    6. OLYMPUS IMT-2 Inverted microscope
- Electroporators:
    1. Lonza amaxa biosystems Nucleofector II
    2. BTX Harvard Apparatus Electro Square Porator + SAFETY STAND 630 B
    3. BIO-RAD Gene Pulser
- A flow cytometer

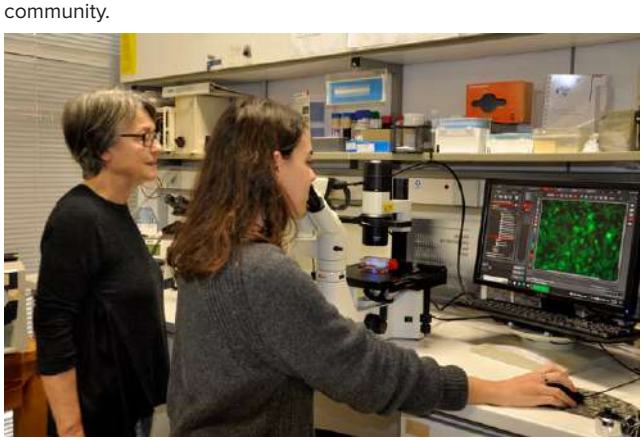
Services

Specialized training and advice for:

- Media preparation, filtration and testing
- Cell culturing and preservation
- Cell Banking in liquid nitrogen
- Mycoplasma detection
- Cell cloning
- Hybridoma production
- DNA transfection
- Toxicity testing
- Mass cell culture using microcarriers, suspension, roller or hollow fiber procedures

Progress and impact in 2022 and 2023

Facility staff has provided support for basic aspects of animal cell culture and specialized training for more than twenty groups from the IMBB, the University of Crete and the broader Greek Biomedical community.



Web page http://www.imbb.forth.gr/en/facilities-en/cells-animals/item/3-animal-cell-culture

Publications The tissue culture facility is acknowledged in a large number of the Institute's publications.

Zaharenia Vlata
Head Of Facility

Takis Makatounakis
Head Of Facility

FACS AND SORTING FACILITY

Summary

IMBB Researchers have full access to the Cell-Sorting Facility of the University of Crete, School of Medicine. The Facility is equipped with **BD FACS Aria III Cell Sorter** capable of 3 Color analysis. The instrument is operated by IMBB personnel Zaharenia Vlata and Takis Makatounakis. The application of the BD FACS Aria III Cell Sorter is available to all research groups of FORTH, the University of Crete and the University Hospital of Heraklion in Crete, providing high quality cell analysis and sorting, technical support and advice for experimental design and specific sorting protocols.

A **FACSCalibur Cell Analyzer** is also installed at the IMBB, supporting the FORTH research community.

Cell- Sorter and Cell Analyzer are flow cytometry tools/applications. Flow cytometry is a technique that detects and measures different populations of cells based on their optical properties (fluorescence). The above technology uses special instruments called flow cytometers, such as FACS (Fluorescence Activated Cell Sorting) and FACS - SORTER.

The FACS function allows the measurement of individual biological particles such as cells, nuclei, chromosomes, etc. An extension of this technology is the sorting of flow cells using the FACS - SORTER, which, in addition to cellular analysis, further isolates cells, bacteria and other particles of a similar size, in living form. The various isolated cells can then be investigated using microscopy, biochemistry and functional experiments.

Equipment

i) **BD FACS Aria III Cell Sorter**

The BD FACSAria III flow cytometer is a high-speed fixed-alignment benchtop cell sorter (https://www.flowcytometry.bmc.med.uni-muenchen.de/best-practice-faq/acquisition/facsaria_user_guide.pdf). With its fixed-optics design and digital electronics, the BD FACSAria III flow cytometer enables multicolor analysis of up to 18 fluorescent and two scatter options at a time. Nearly all cytometer functions are operated from within BD FACSDiva software.

BD FACSAria III flow cytometer utilizes three lasers: **1) Violet - 405nm, 2) Blue - 488nm and 3) Red Diode - 633nm**. Several common fluorochromes (FITC, Alexa Fluor 488, R-PE, PE-Texas Red, PerCP, PerCp-Cy5.5, PE-Cy7, APC, APC - Cy5.5, BD Horison VPD450, BD Horison Brilliant Violet 421, Pacific Blue, DAPI etc) and fluorescent GFP protein have been successfully used.

ii) **FACSCalibur**

FACSCalibur is a top-of-the-line cell analyzer with two lasers:

1. **488 nm Ion Laser Blue**-Green Argon,
2. **633 nm Red** Helium Neon laser.

FlowJo software is installed on a computer near to the FACSCalibur to analyze flow cytometry data.

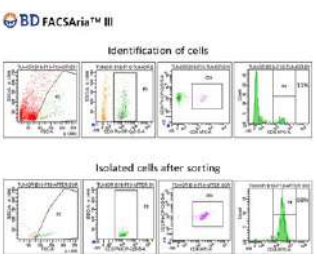
Three fluorescence channels and two scatter channels are available from the 488 nm laser (FSC, SSC, FL1, FL2, FL3). One fluorescence channel is available from the 633 nm laser (FL4).

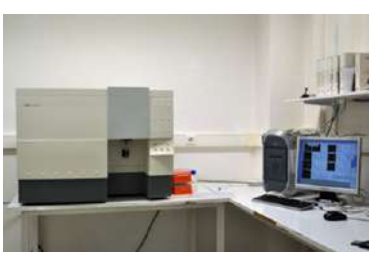
Progress in 2022-2023

The BD FACS Aria III Cell Sorter operated 22 days a month and provided cell sorting services in 8 laboratories of FORTH, 15 of the University of Crete and 9 of the University Hospital of Heraklion.

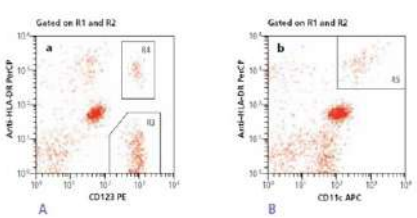
FACSCalibur continued to provide technical assistance to FORTH researchers by conducting flow cytometry-based analysis.

I.BD FACS Aria III Cell Sorter





II.FACSCalibur



A Region R3 defines basophils and region R4 defines CD123+ DCs (0.14% of total).
B Region R5 defines CD11c+ DCs (0.21% of total).

Web page http://www.imbb.forth.gr/en/facilities-en/cells-animals/item/6-facs-sorting

Kriton Kalantidis
Head Of Facility

GREENHOUSE - CONTROL ENVIRONMENT ROOMS UNIT
GREENHOUSE AND GROWTH CHAMBER FACILITIES

The Plant groups of IMBB have full access to a glasshouse facility, located in cooperation with the University of Crete located at the nearby University campus. The glasshouse is composed of 12 independent chambers of a total of 540m2 net surface. All chambers are air-conditioned and have been capacitated with an automatic watering system. The greenhouse has the capacity to run at a P2 safety level, it is capacitated with a negative pressure and seed-filtering sewage systems and an autoclave facility for all organic waste.
Two chambers of a total 120m2 have an additional plant-growth light system installed. In addition, attached to the greenhouse there is a preparation room and warehouse. The greenhouse is supported by a full time greenhouse IMBB technician. Within the last two years a large number of experiments have run in the glasshouse with a wide rage of model and non model plants. Research experiments in the glasshouse included, work on the fields of plant pathogen and plant pest interactions, plant stress responses, CRISPR mutant generation, plant genetics and plant genomics amongst other. Additionally, the plant groups have access to numerous high end growth chambers with fully controlled environment.

Individual air-conditioned chambers with light support. Here with tobacco plants

Dimitris Dialektakis
Head of Facility

FACILITY MEMBERS

Research assistants:
Xrysoula Vamvakia
Xara Giata

MINOTECH BIOTECHNOLOGY

Summary
MINOTECH biotechnology (Mb) is the in-house biotechnology production facility of IMBB-FORTH and has over 30 years of experience specialized in production of bacterial-derived proteins. Mb produce a wide array of high purity and superior quality Restriction Endonucleases, DNA Modifying Enzymes and Molecular Weight Markers that aim to meet the needs of scientists engaged in Research, the Biotechnology Industry and the Clinical Laboratory. Mb products are cited in more than 200 peer-reviewed publications and are supplied to customers directly or under OEM agreements through major European, Asian and North American distributors.
Mb is active in the production of Molecular Biology tools and is highlighted as one of the 16 international suppliers of Restriction Enzymes (REs) in the largest database on REs (REBASE, rebase.neb.com).

Capabilities
MB facility offer

- Large scale (mg to gram) protein purification of tagged or untagged proteins.
- Controlled production of biomass (mainly microbial) over a wide range of controlled conditions (culture media, temperature, pH, aeration, stirring, etc).

Web page https://www.minotech.gr

Kyriaki Sidiropoulou
Head of Unit

ELECTROPHYSIOLOGY UNIT

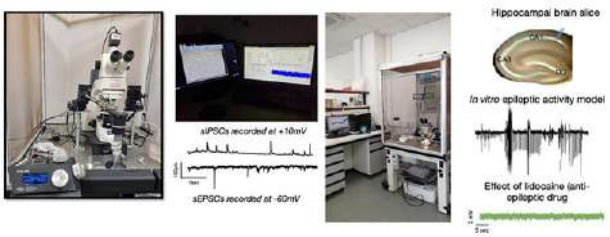
Description

The electrophysiology unit contains all the necessary equipment for performing both field and patch-clamp recordings from brain slices and/or cell cultures. The services provided include the experimental design, the actualization of the experiments and data analysis on the following:

a) short-term and long-term plasticity experiments from brain slices of various cortical areas, the hippocampus or amygdala
b) current-clamp recordings to study neuronal excitability, spontaneous or evoked synaptic responses from brain slices with pharmacological applications if necessary.
c) recordings can also be performed from YFP or GFP- labeled cells, either from brain slices or neuronal cultures
d) voltage-clamp recordings to study spontaneous excitatory and/or inhibitory activity from brain slice or cell cultures

Progress in 2022-2023

During 2002 and 2023, we have increased our experimental efficiency by having 2 rigs for electrophysiology recordings. One specifically for field recordings and one dedicated to patch-clamp recordings. Concurrently, we have developed two electrophysiological protocols in order to screen for drugs that alter neuronal excitability and synaptic plasticity. We are currently using these capabilities to collaborate with other academic labs but also pharmaceutical companies.



(Left side) Part of the patch-clamp rig along with indicative recordings of spontaneous inhibitory and excitatory postsynaptic currents (sIPSC and sEPSC). (Right side) The field recordings rig along with indicative recordings of the in vitro epileptic activity model and the effect of lidocaine.

Web page	https://www.imbb.forth.gr/imbb-people/en/electrophysiology-unit-home
Publications	Kalemaki K, et al. (2022) The developmental changes in intrinsic and synaptic properties of prefrontal neurons enhance local network activity from the second to the third postnatal week in mice. **Cereb. Cortex** 32(17):3633-3650 doi: 10.1093/cercor/bhab438
	Thomaidi M, et al. (2022) Local anaesthetics via multicomponent reactions. **ChemMedChem** 17(15): e202200246 doi: 10.1002/cmdc.202200246
	Rogdakis T, et al. (2022) Development and biological characterization of a novel TrkA agonist with neuroprotective properties against amyloid toxicity. **Biomedicines** 10(3):614 doi: 10.3390/biomedicines10030614

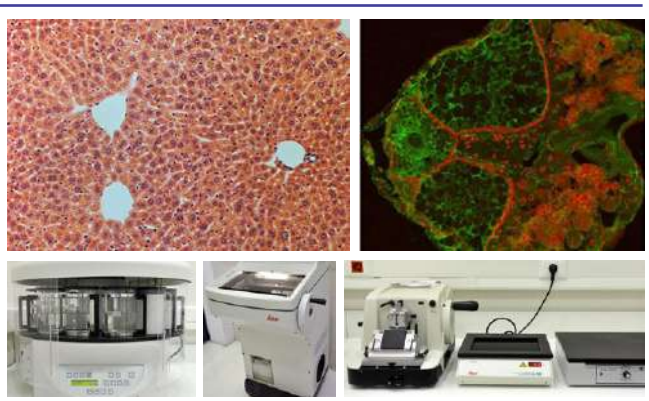
Marina Koukaki
Head of Unit

HISTOLOGY UNIT

The Histology Lab is a Support Unit of IMBB equipped with Automatic Tissue Processor (Leica TP1020; Paraffin Embedding Station (Leica EG1150H)-Cold Plate (Leica EG1150C); Rotary Microtome (Leica RM2125) and (RM2255) - Water bath for Paraffin Sections (Leica HI1210) - Flattening Table for Clinical Histopathology; Cryostat with UVC Disinfection (Leica CM1850UV); and Stereo Microscope (Leica M125). The Unit provides technical support and Training to perform histology and Immunocytochemistry experiments on frozen sections or paraffin embedded material.

Progress and impact in 2022 and 2023

The lab provided assistance for fifteen Research Groups of IMBB and the wider Biomedical Research Community of Herakleion. Twenty five scientists were trained in histological analysis protocols.



Grants

Grants

COMPETITIVE GRANTS AWARDED IN 2022-2023 (*Coordinator)

EU PROGRAMMES

EIT Health, EpiDEMPrev - Ageing@EITHealth PhD School, 18.000,00 € (total grant budget: 46.200,00 €), 2022-2023, **N. Tavernarakis**

ERA Chair, HORIZON-WIDERA-2022-TALENTS-01, MicroBioPest - Microbial Biopesticides to Control Disease Vectors and Agricultural Pests, 2.500.000,00 €, 2023-2028, **J. Vontas* (ERA Chair: G. Dimopoulos)**

ERC-2021-ADG, CorticalCoupling - Dendro somatic Coupling and global neuronal signaling, 196.250,00 € (total grant budget: 2.500.000,00 €), 2023-2027, **P. Poirazi**

ERC-2022-STG, NEURACT - Untangling population representations of objects. A closed loop approach to link neural activity to mouse behavior, 1.900.000,00 €, 2023-2028, **E. Froudarakis***

HORIZON-CL6-2022-FARM2FORK-01, RATION - Risk Assessment Innovation for low-risk pesticides, 266.500,00 € (total grant budget: 6.994.748,00 €), 2022-2026, **J. Vontas**

HORIZON-CL6-2023-FARM2FORK-01, NextGenBioPest - Next Generation Biopesticides for the control of the most "difficult-to-manage" pests and pathogens inf fruits and vegetables, 1.024.375,00 € (total grant budget: 5.671.625,00 €), 2023-2028, **J. Vontas***

HORIZON-CL6-2023-ZEROPOLLUTION-01, AquaBioSens - On-site biological sensing for aquatic pollutants and biohazards, 917.000,00 € (total grant budget: 2.470.992,50 €), 2023-2026, **E. Gizeli***

HORIZON-EIC-2022-PATHFINDEROPEN-01, SoftReach - Minimally-Invasive Soft-Robot-Assisted Deep-Brain Localized Therapeutics Delivery for Neurological Disorders, 568.750,00 € (total grant budget: 2.158.000,00 €), 2023-2026, **I. Charalampopoulos***

HORIZON-HLTH-2023-TOOL-05, UniHealth - Development of a global diagnostic ecosystem for detecting and monitoring emergency-prone pathogens across species and in a unified way, 1.283.488,75 € (total grant budget: 4.887.345,13 €), 2023-2027, **E. Gizeli***

HORIZON-INFRA-2021-EMERGENCY-02, ISIDORe - Integrated Services for Infectious Disease Outbreak Research, 187.500,00 € (total grant budget: 20.998.624,00 €), 2022-2025, **J. Vontas**

HORIZON-MSCA-2021-DN-01, TClock4AD - Targeting Circadian Clock Dysfunction in Alzheimer's Disease, 240.098,40 € (total grant budget: 3.811.636,00 €), 2023-2027, **N. Tavernarakis**

HORIZON-MSCA-2021-PF-01, GinieEffect - GABAergic INterneurons signaling ImbalancE; A promising target underlying PFC-dependent cognitive flexibility defect, 153.486,72 €, 2022-2024, **P. Poirazi***

HORIZON-MSCA-2021-SE-01, INOVEC - A research and InNOvation Partnership for enhancing the surveillance and control of mosquito VECtors of emerging arboviruses, 133.400,00 € (total grant budget: 1.407.600,00 €), 2023-2026, **J. Vontas**

HORIZON-WIDERA-2022-ACCESS-04, CHAngeing - Connected Hubs in Ageing: Healthy Living to Protect Cardiovascular Function, 1.370.000,00 € (total grant budget: 4.999.693,75 €), 2023-2026, **N. Tavernarakis**

HORIZON-WIDERA-2022-TALENTS-04, UnfearHD - Unfolding the early Htt aggregates: an interdisciplinary approach for characterizing novel molecular events that impact Heat Shock Response in Huntington Disease, 169.326,72 €, 2023-2025, **N. Tavernarakis***

GREEK PROGRAMMES

GSRI's Flagship Project, Brain Precision - National research network to elucidate the genetic basis of Alzheimer's and Parkinson's neurodegenerative diseases, detect reliable biomarkers, and develop innovative computational technologies and therapeutic strategies based on precision medicine, 1.444.000,00 € (total grant budget: 2.274.000,00 €), 2023-2025, **N. Tavernarakis & G. Garinis***

GSRI's Flagship Project, INNOPP - Innovations in Plant Protection for sustainable and environmentally friendly pest control, 1.110.000,00 € (total grant budget: 4.915.000,00 €), 2023-2025, **J. Vontas***

Hellenic Foundation for Research and Innovation, EPINSCTUDR (4532) - Epigenomic profiling of a neural stem cell tumour in Drosophila, 199.940,00 €, 2022-2025, **C. Delidakis***

Hellenic Foundation for Research and Innovation, INSIGHT (4049) - From population representations to perception and action. A closed loop framework to study object recognition in mice, 199.900,00 €, 2022-2025, **E. Froudarakis***

Hellenic Foundation for Research and Innovation, AcouBioCoV (4969) - Acoustic biosensor for rapid and sensitive COVID-19 antibodies detection in whole blood and at the point-of-care, 81.432,00 € (total grant budget: 99.576,00 €), 2022-2023, **E. Gizeli***

Hellenic Foundation for Research and Innovation, ALANTIN (7054) - Exploring a novel role of Albumin Antimicrobial Immunity, 120.000,00 €, 2022-2024, **I. Morianos***

Hellenic Foundation for Research and Innovation, AdvanceCarob (16713) - Advancing Carob research; Science in the service of a tarditional and resilient cultivation, 90.300,05 € (total grant budget: 167.900,05 €), 2023-2025, **K. Kalantidis***

Hellenic Foundation for Research and Innovation, PyrethroidRes (7406) - Unravelling the importance of sodium channel mutations in resistance to contact and volatile pyrethroids in the malaria vector Anopheles gambiae, 120.000,00 €, 2023-2024, **L. Grigoraki** *

Hellenic Foundation for Research and Innovation, TraMeCaR (19067) - Dissecting the molecular mechanism and physiological role of Golgi-bypass as a major mechanism of subcellular protein trafficking, 99.660,00 €, 2023-2025, **G. Diallinas***

Hellenic Foundation for Research and Innovation, GliaAge (16399) - Deciphering the role of glial autophagy in neurophysiology and ageing using in vivo chemo-optogenetics, 400.000,00 €, 2023-2025, **N. Tavernarakis***

Hellenic Foundation for Research and Innovation, MAYA (14772) - Investigation of the protective roles of caloric restriction mimetics in myelin disruption via a novel, non-invasive advanced imaging approach, 200.000,00 € (total grant budget: 399.970,00 €), 2023-2025, **D. Karagogeos***

Hellenic Foundation for Research and Innovation, NeuroFlame (15546) - Delineating the impact of DNA damage on Neuroinflammation during Aging, 125.000,00 € (total grant budget: 400.00,00 €), 2023-2025, **N. Tavernarakis**

Hellenic Foundation for Research and Innovation, THESEUS (14779) - Modeling Transcription: an integrated approach to understand cancer-specific gene expression programs, 359.941,00 € (total grant budget: 399.987,00 €), 2023-2025, **N. Poulakakis***

Hellenic Foundation for Research and Innovation, TRANS-MOD (15276) - Modeling Transcription: an integrated approach to understand cancer-specific gene expression programs, 270.661,00 € (total grant budget: 400.000,00 €), 2023-2025, **I. Talianidis***

Hellenic Foundation for Research and Innovation, FIT (15828) - Deciphering the role of Cancer Associated Fibroblasts in immunotherapy resistance and tumor metastasis, 200.000,00 € (total grant budget: 321.800,00 €), 2023-2025, **P. Verginis***

Hellenic Foundation for Research and Innovation, MalVec (16044) - Improving the sustainability of malaria vector control, 280.000,00 € (total grant budget: 400.000,00 €), 2023-2025, **J. Vontas***

Hellenic Foundation for Research and Innovation, APOE-META-BRAIN (15529) - Elucidating the impact of apolipoprotein E and metabolic comorbidities on the pathogenesis of Alzheimer's Disease, 210.800,00 € (total grant budget: 400.000,00 €), 2023-2025, **D. Kardassis***

Hellenic Foundation for Research and Innovation, COFLEX (14941) - Mechanisms of cognitive flexibility across primates, rodents and machines, 200.000,00 € (total grant budget: 400.000,00 €), 2023-2025, **P. Poirazi**

Ministry of Rural Development and Food, Sub-Measure 16-DaCuS - An alternative method of olive fruit fly management, through the control of the symbiotic bacteria of Bactrocera oleae, 70.000,00 € (total grant budget: 283.165,04 €), 2023-2025, **J. Vontas**

National Public Health Organization, Mosquitos Laboratory analysis of mosquitoes in the framework of enhanced entomological surveillance in the Prefecture of Crete for 2023, 16.900,00 €, 2023-2024, **J. Vontas***

National Recovery and Resilience Plan (Greece 2.0), EDIMO-SUB3. Applied Research for Precision Medicine through a Non-Profit Organization (NPO) under Private Law – "Hellenic Precision Medicine Network" (HPMN), 984.171,07 € (total grant budget: 3.779.666,96 €), 2023-2025, **N. Tavernarakis & C. Stratakis***

Region of Crete, Scientific support for plant protection and vector control programmes, 185.000,00 €, 2023-2026, **J. Vontas***

State Scholarships Foundation, Hubert Curien - Regulation of the (patho)physiological adaptive immune response from SATB1 genome organizer, 10.000,00 €, **C. Spilianakis***

OTHER INTERNATIONAL PROGRAMMES

HFSP Research Grant, Cellular and molecular basis of bilaterian symmetry, 368.935,62 € (total grant budget: 1.106.806,86 €), 2023-2026, **A. Pavlopoulos***

National Health and Medical Research Council, CorticalEngrams-The role of memory engrams in the cortex, 115.942,00 € (total grant budget: 656.131,09 €), 2022-2024, **P. Poirazi**

National Institutes of Health, GIRK Epilepsy-Dravet Syndrome Anti-Epileptic Control by Targeting GIRK Channels, 75.219,69 € (total grant budget: 647.790,22 €), 2022-2027, **K. Sidiropoulou**

Worldwide Cancer Research, Genetic Dissection of Factor Contributing to Disease Severity in a Fly Brain Tumor Model, 200.306,89 €, 2022-2025, **C. Delidakis***

Grants

PRIVATE FUNDING

Adama, Validating the selectivity and efficiency of insecticide formulations and mixtures, using classical and biotechnology based approaches, 85.684,00 €, 2023-2024, **J. Vontas***

Bayer, PestPoC/Caco-2, 300.000,00 €, 2022-2024, **J. Vontas***

Fondation Sante, Neuroflame - Delineating the impact of DNA damage on neuroinflammation during aging, 50.000,00 €, 2023-2025, **G. Garinis***

Fondation Santè, Leismaniasis - Functional Analysis of Insecticide Resistance Mechanisms in Major Leishmaniasis Vectors in South East Mediterranean, 50.000,00 €, 2022-2023, **K. Mavridis***

Fondation Santè, Mechanistic understanding of long non-coding RNA chromatin (dis-) association in human cells, 50.000,00 €, 2022-2024, **E. Ntini***

Fondation Santè, Deciphering the role of Notch signaling in regulatory T cells: a novel “checkpoing” during tumor development, 50.000,00 €, 2023-2025, **P. Verginis***

Institute of Pharmaceutical Research and Technology, Neuroiflammation-on-chip - Development of a novel three dimensional (3D) platform for modelling human neuroinflammation and utilization of its potential for drug screening, 121.000,00 €, 2023-2025, **I. Charalampopoulos***

K&N Efthymiadis-Single Member S.A., Botrytis cinerea-Development of a molecular methodology employing qcLAMP for the detection of the plant borne pathogen Botrytis cinerea in tomato samples using the portable Pebble device (BIOPIX-T) for field-based detection, 13.900,40 €, 2023-2024, **E. Gizeli***

Pharmaserve-LILLY, Planning of training-educational activities, seminars, conferences and training of new postgraduate and doctoral researchers, 20.000,00 €, 2022-2024, **P. Sidiropoulos***

Pharmathen, Research collaboration of the Laboratory of Genomic Instability IMBB-FORTH, 75.000,00 €, 2023-2025, **G. Garinis***

Uni-Pharma, Development of a non-steroidal, exosome based anti-inflammatory strategy, 75.000,00 €, 2023-2025, **G. Garinis***

Administration

Many thanks to our Administration and Support Personnel

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Executive secretary

Rodanthi Lasithiotaki
Secretary

Sofia Foukaraki
Secretary

Nikos Bourtzis
Administrative Assistant

Nektaria Kelaidi
Accounting

Manolis Grigorakis
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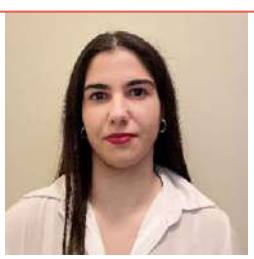

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