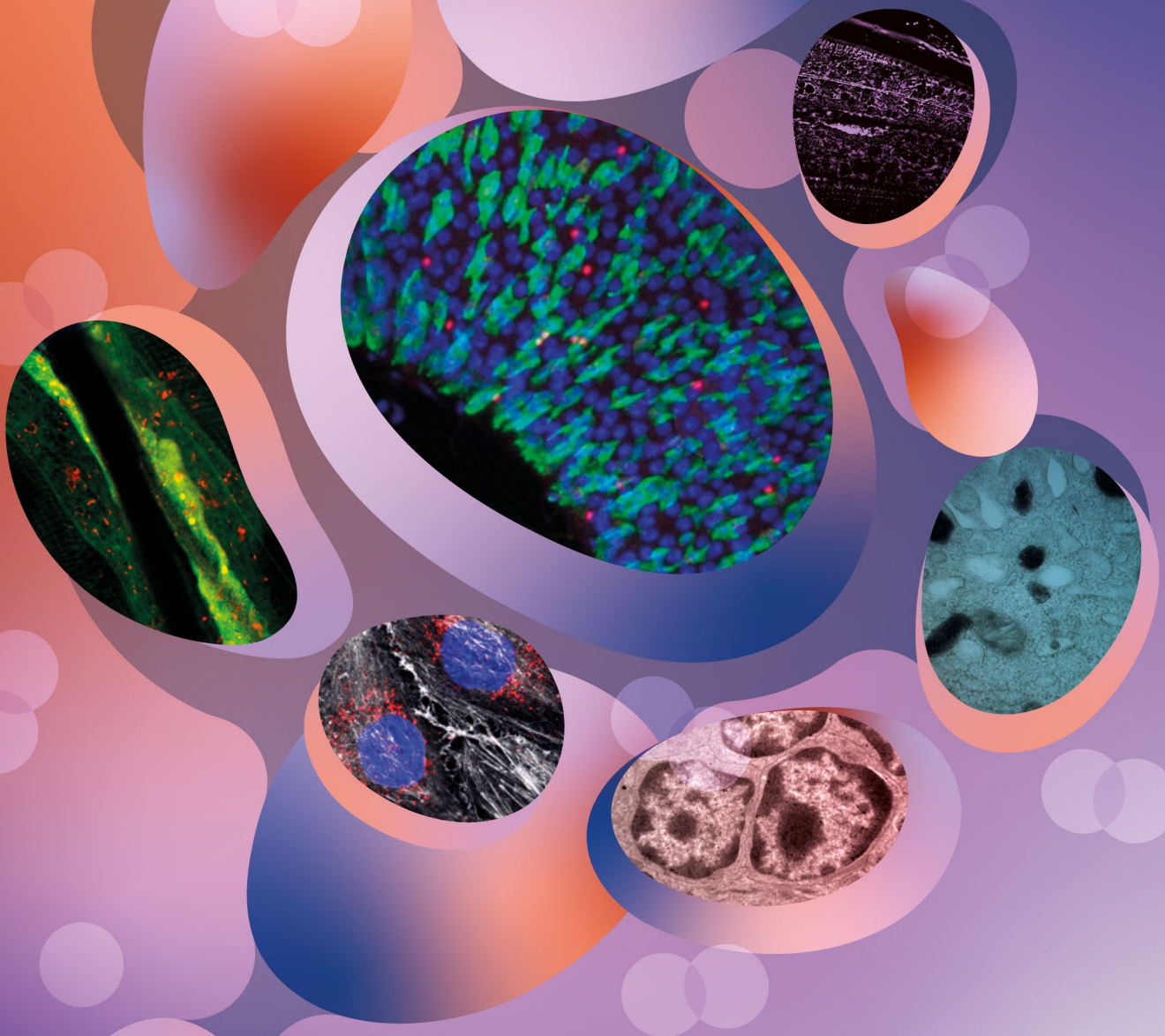
INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY

BIENNIAL REPORT 2024-2025



FORTH
FOUNDATION FOR RESEARCH AND TECHNOLOGY - HELLAS

INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY

BIENNIAL REPORT

2024-2025

FORTH

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Vision

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

IMBB is strongly dedicated to preserve as one of the leading Greek research institutes with a significant presence in the European and worldwide science ecosystem. To this end the continuous development of the Institute must reflect the rapid transformation of research into new subject areas and technologies as well as changing priorities of international and national funding programs. As this report shows we have been successful in meeting these challenges and we are looking forward to the future with confidence that we, thanks to our strong foundations, can continue to achieve our ambitious goals. In 2024-2025, IMBB researchers have published in top scientific journals, attracted major grants, earned distinctions and developed impressive collaborations and networks worldwide. A measure of our good reputation is the fact that eminent scientists from abroad are keen to take up positions at IMBB, while many talented international young researchers join, thanks to leading-edge research initiatives, as well as training and mentorship programs.

Science

The publication record of IMBB not only reflects the scientific excellence of IMBB but also the different subject areas covered. Among the prominent publications in 2024-2025 are notably eight papers in Nature Communications, as well as additional ones in other top-ranking journals such as PNAS, Nature Neuroscience, and Nature Cell Biology; they are summarized in Highlights (page 13). IMBB Researchers have made key discoveries in different research areas. In neuroscience, three publications examined dendrites (branches of neurons): how they link memories across time, how artificial neural network can incorporate features of dendrites, and how potassium ions modulate dendritic integration. Several papers discussed how different processes in humans affect health and ageing. One revealed how DNA damage in the brain's immune cells sparks inflammation. Two studies linked transcription problems to ageing, and showed why proteostasis collapses during ageing. Spermidine was established to regulate the autophagic response to fasting. With relevance to cancer, it was discovered that cytoplasm fragments internalize into the nucleus. Investigations looked at the role in Systemic lupus erythematosus of a chromatin factor with a link between sex bias and inflammation, and how cancer-associated fibroblasts affect cancer outcome. The regulation of intestinal stem cells by epigenetic factors was revealed in the *Drosophila* model. Metacaspase enzymes were shown to be required for the longevity of plant seeds. Finally, the development of resistance against a new generation of insecticides in mosquitoes transmitting malaria was reported.

People

The Institute has welcomed new group leaders. Eirini Skourtanioti, an outstanding population geneticist trained at the Max Planck Institute for Evolutionary Anthropology in Leipzig and Ludwig-Maximilians-Universität München, was elected as a new Group Leaders at IMBB in 2025. She has a strong background in ancient DNA analysis and human population genetics and has published widely cited studies on Neolithic and bronze age human populations as well as how pathogens have influenced human history. Her expertise bridges ancient human genomics and its integration with historical and bioarchaeological evidence. Two collaborative faculty members from University of Crete joined the Institute during this period. Ioanna Keklikoglou is investigating resistance to therapies in cancer and Dapne Bazopoulou studies ageing in the model system *Caenorhabditis elegans* IMBB was also strengthened by a new collaborative Researcher Dimitris Tzeranis with expertise in the area of biomaterials. Nicholas Katsanis with experience in the field of genetics, cell biology, and drug discovery, also joined IMBB as an Adjunct Researcher. Finally, Manolis Pasparakis joined IMBB in 2025 as an ERA-Chair to strengthen research in the area of the mechanisms regulating inflammation.

As during previous years many of the core personnel have retired during these two years. Their expertise is unfortunately lost, as there are few new positions created due to government restrictions.

Awards and distinctions

Christos Delidakis and John Vontas were elected as new EMBO members in 2024. The scientific excellence of Nektarios Tavernarakis was recognized by the award of an Honorary Doctorate from Ionian University and the election as President of the European Molecular Biology Conference (EMBC). Domna Karagogeos received the Academy of Athens Award in the field of "Multiple Sclerosis".

Funding

Recognition of IMBB's excellence is its success in attracting major funding from national and international sources. All grants awarded to IMBB researchers in 2024 and 2025 are listed on page 107. Among the most prestigious grants are an ERC consolidator grant and funding from H.F.R.I.-SNF for excellence performance in ERC Advanced, two major international grants (European Union and Human Frontier Science Program) for studies of ticks as vectors of infectious diseases, as well as several grants from the European Union Horizon programme for research on insects of agricultural interest and from Gates foundation for studies on malaria transmitting mosquitoes. IMBB was also awarded and coordinated an Excellence Hub grant, for developing diagnostics for infectious diseases (DxHub).

In addition, IMBB participated in several national funding programs (GSRI Flagship and HFRI programs), which had a positive impact on the IMBB financial figures.

Innovation and collaboration with private sector sector (Pharma and Agrochemical companies) has also successfully been pursued in this period.

Facilities and equipment

We strive to maintain and continuously upgrade our core facilities to current best practices. The Animal House has been strengthened. We have also managed to secure funding for updating our omic units, including a state of the art Mass

Spectrometry instrument, expected in 2026 at IMBB. New fully equipped insectaries for transgenic arthropod vectors and experimental infections work (Animal Containment Level 2 & 3) have been built. This is a major investment for future research in vector – pathogen biology, funded by an ERA Chair grant.

A Bioinformatics Unit has been established at IMBB, including space and equipment, aiming to advance and provide bioinformatics expertise and computational support to IMBB researchers as well as advice on the organization, sharing and the long-term use of bioinformatic data according the FAIR principles.

The National infrastructure programs, and other on-going efforts, are expected to kick off in 2026 and will substantially help IMBB further pursue these developments and equipment renewal (computational, cell cultures, bioimaging, omics).

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

The association with EU-Life allowed us to further pursue the implementation of 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.

Importantly, IMBB/FORTH participates in the EU funded project INCLUDE aiming to advance intersectional gender equality in the BioMedical Research and Innovation (R&I) sector.

The Mentoring and Career Track Scheme at IMBB was initiated by IMBB vice Director Electra Gizeli who set up the main pillars of the scheme. Currently Tassos Pavlopoulos is in charge of the program. For details see page 28. The aim of the program is to guide young scientists (Ph.D. students, post-doctoral scientists) to achieve their optimal career path by providing career guidance by experienced people from the academic, public and private sectors as well as access to courses in complementary skills. The program is much appreciated by the younger scientists and there are tangible results from the activity.

Outreach activities

IMBB participated in Researchers Nights at FORTH in 2024 and 2025 whereby more than two thousand people join us giving the opportunity to young researchers to explain their research projects to a wide audience. IMBB also has a presence in events such as exhibitions and innovation days. The Institute has a significant presence in TV, radio, press and social media, and its researchers are actively involved in FORTH outreach activities such as podcasts and public discussions. An organized program welcomes high school students to visit IMBB introducing them to biological science. For more details see page 31.

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 (page 37). A site visit takes place every 3-4 years whereby all group leaders present their scientific progress and the committee meet the Director for extensive discussions. The outcome of the last evaluation was overall positive for the achievements of the Institute and constitutes the basis for the strategy of future developments.

Looking to the future

We look into the future with optimism, powered by a dynamic IMBB team within FORTH and the University of Crete Ecosystem, with many ideas and constructive interactions among our staff and the international scientific community.

Challenges

IMBB is critically dependent on competitive grants from international, EU and national sources. Horizon Europe, from which a majority of our external funding originated, is now entering its final two years and the next Framework Program 10 is now being finalized. The major changes will be stronger emphasis on top-down approaches as well as innovation. IMBB must adjust to this new funding landscape and this will require new priorities in our research. The fact that many funding instruments are now focusing on specific areas such as defense is a threat to the future of IMBB. In addition, the number of government-funded well trained permanent employees are steadily decreasing.

The future

IMBB will aim to strengthen strategic thematic directions with critical mass (for example neurosciences and gene regulation) and synergies with the research ecosystem, and others with geographical relevance and international perspectives for the Institute. Ancient DNA, in areas which bridge genomics and its integration with historical and bioarchaeological evidence, Vector Biology including work on transgenic arthropods and interactions with vector borne diseases in the new facilities, and artificial Intelligence in Molecular Biology and Biotechnology are some of the target areas for the next strategic period.

The main priority is always to continue to attract young talented researchers as new group leaders. And to do so, IMBB must provide competitive environment and facilities that match the research areas of the applicants for new positions.

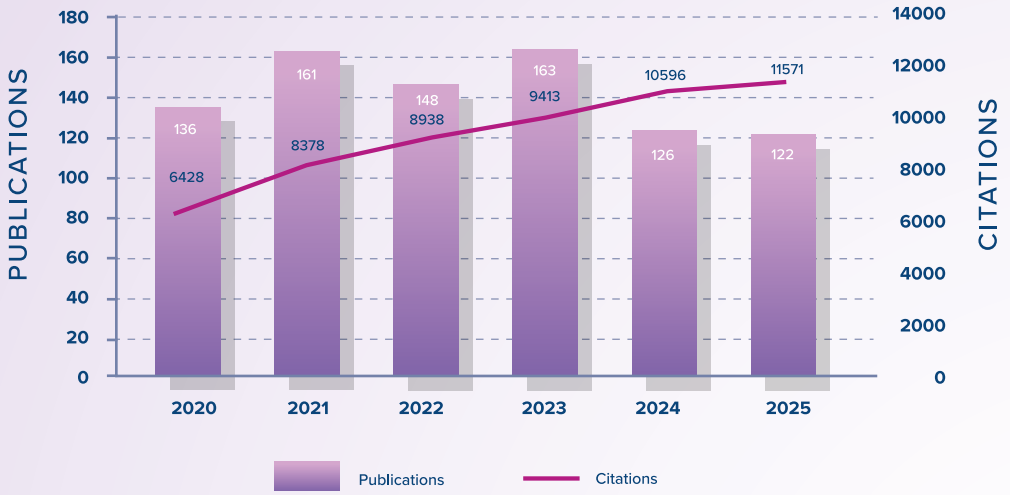
We will provide support for high quality applications for funding (ERC/ERC Synergy, WIDERA, HFSP) and also adjust to a new funding landscape with emphasis on innovation and thematic directions, even if this requires some adaptations or even new priorities in our research. Researchers will have to become more familiar with “dominant” innovation funding instruments like PATH Finder and EIC acceleration programs, and we will try to facilitate that, via strengthening collaborations and highlighting successful paradigms.

Finally, we will further consolidate our program for mentoring and support of early-stage researchers and further organize efforts to guide new scientists and help them realize the next step of their career.

Facts & Figures

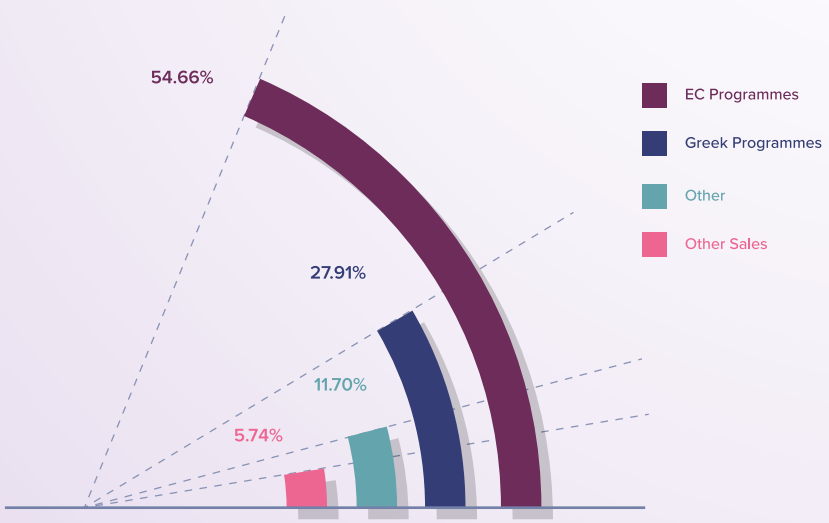
Facts & Figures

Publications & Citations

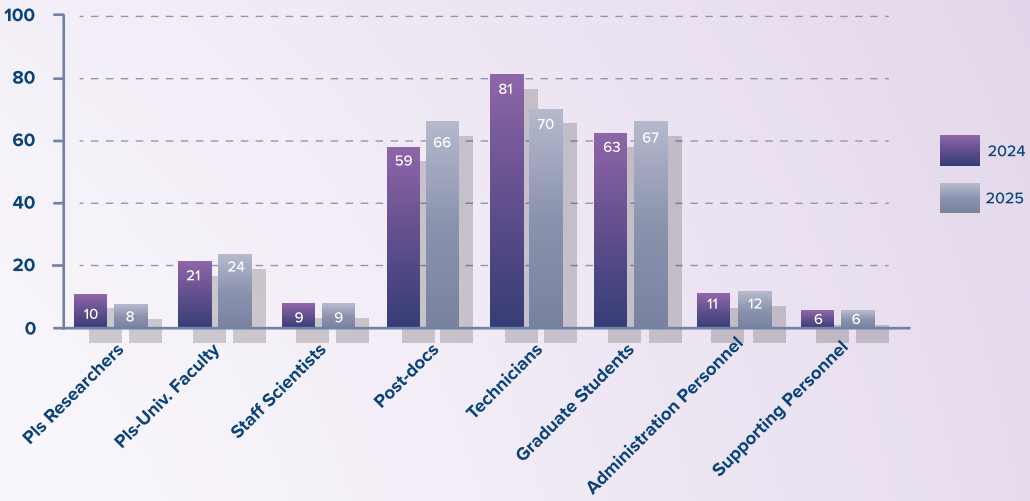


Annual Turnover

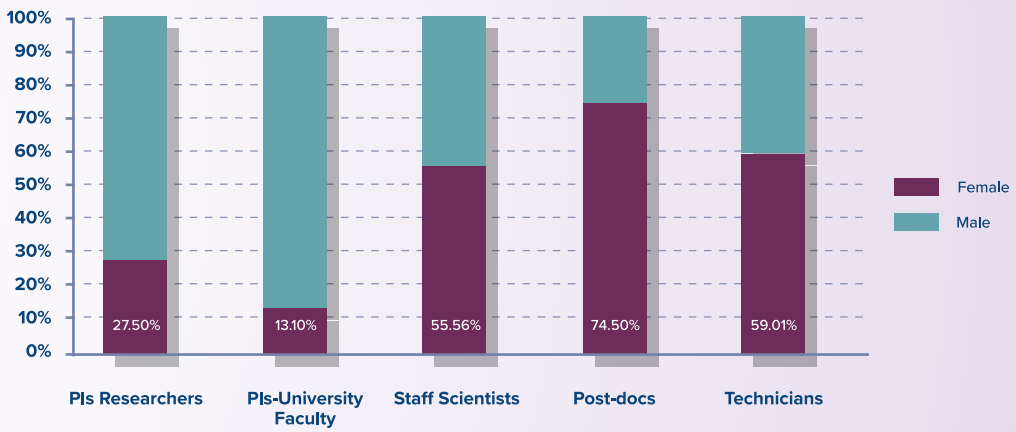
Funds & Grants 2025



IMBB Personnel in 2024 & 2025

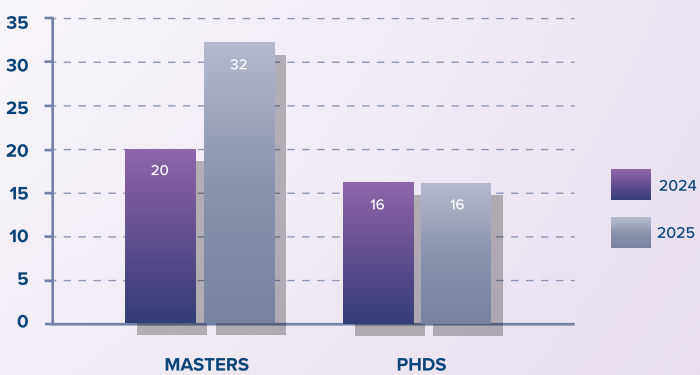


Gender distribution of research staff 2024 - 2025



Data labels are percentages of female staff

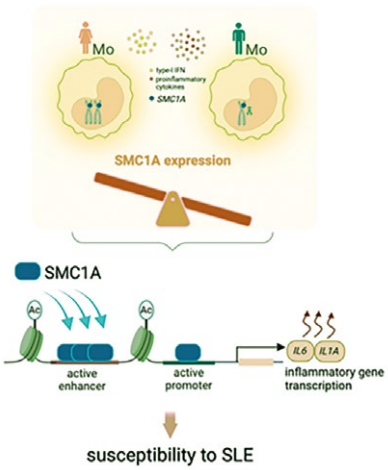
Masters & PhD degrees awarded



Scientific Highlights

Scientific highlights

SMC1A/cohesin as a mediator of sex-biased immune responses

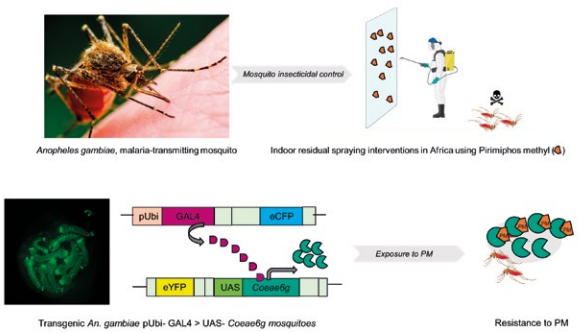


SMC1A, an X-linked cohesin subunit and chromatin architectural factor, has been identified a potential mechanistic link between sex bias and inflammatory dysregulation in systemic lupus erythematosus (SLE). Researchers led by Professor Bertsias at the Laboratory of Rheumatology, Autoimmunity and Inflammation at the University of Crete Medical School and IMBB-FORTH, together with collaborators from the Biomedical Sciences Research Center 'Alexander Fleming', showed that SMC1A is more highly expressed in monocytes from women with SLE than in those from men with SLE, healthy individuals, or patients with ankylosing spondylitis, a non–sex-biased autoimmune disease. Under lupus-relevant inflammatory stimulation, SMC1A is redistributed to active enhancers of immune and inflammatory genes, where it appears to promote their transcription. This enhancer-associated activity is linked to increased expression of lupus-relevant inflammatory pathways and higher secretion of cytokines such as IL-6, supporting a direct role for SMC1A in amplifying monocyte activation. Functionally, the work suggests that SMC1A is not simply a marker of sex-biased expression, but a disease-relevant chromatin regulator that helps shape the pathogenic inflammatory program of lupus monocytes. The significance of the study lies in moving beyond descriptive sex differences toward a specific epigenetic and transcriptional mechanism that could help explain why inflammatory pathways are accentuated in women with SLE and may eventually inform new therapeutic strategies targeting chromatin-mediated immune activation.

Kosmara, D., et al. (2025) ***Nature Communications*** *16:10350*

Mosquito vectors of malaria rapidly develop resistance against new generation insecticides

More than half a million people, to their vast majority children under the age of five, die annually due to malaria, with Sub-Saharan Africa and south-east Asia being the most highly burdened regions. Mosquitoes belonging to the genus *Anopheles* carry *Plasmodium* parasites and infect humans. Control of the mosquito vector by means of insecticides has greatly contributed to malaria elimination so far; nevertheless, these successful efforts are seriously undermined by the rapid development and spread of insecticide resistance in the mosquitoes. Understanding the molecular basis underlying these resistant phenotypes is crucial to ensure the effectiveness and sustainability of the currently available malaria control interventions.

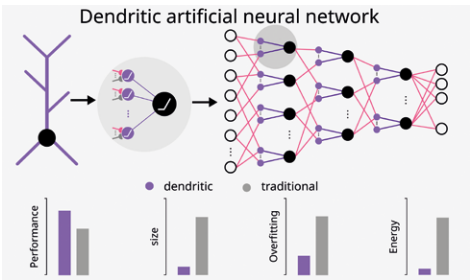


A study by Dr. Sofia Balaska and Dr. Linda Grigoraki in the Molecular Entomology group at IMBB led by Professor John Vontas, and carried out in close collaboration with the Liverpool School of Tropical Medicine in the UK, revealed a novel carboxylesterase-mediated mechanism of cross-resistance to insecticides in *Anopheles gambiae*. In this work a predictive chemo-proteomic framework was developed to identify enzymes that can bind to insecticides. The study first investigated Actellic300S (microencapsulated Pirimiphos methyl - PM) a new, highly effective insecticide formulation, recently introduced in malaria control campaigns in Africa after many years of development. Application of the methodology revealed that the carboxyl-esterase Coeae6g is capable of binding to the active insecticidal molecule. Using genetic modification approaches and biochemical characterization, it was proven that Coeae6g acts like a sponge binding PM, and prevents it from reaching its final molecular target in mosquito's nervous system. Transgenic mosquitoes over-expressing Coeae6g display a resistant phenotype against PM, via this sequestration mechanism. Furthermore, Coeae6g was shown to act in a similar way on a variety of different insecticides, widely used in vector control interventions, leading to high levels of resistance and cross resistance.

Given that the novel Actellic300S formulation is at the moment among the cornerstones of malaria vector control strategies, the findings of this study have important implications for malaria prevention efforts. Coeae6g has already been detected at higher levels in several *Anopheles* field populations in Africa, posing a threat on malaria control.

Balaska, S., et al. (2025) ***Nature Communications*** *16:10772*

Artificial Neural Networks with Dendrites: A Solution for Energy-Hungry AI Systems



Researchers at IMBB have developed a new type of artificial neural network (ANN) that incorporates features of biological dendrites. This innovative design allows for accurate and robust image recognition while using significantly fewer parameters, paving the way for more compact and energy-efficient AI systems.

AI plays a crucial role in driving innovation and improving efficiency, offering smarter solutions to complex problems and enhancing our daily lives. However, current AI systems are huge, comprising millions-to-billions of parameters, thus consuming massive amounts of energy, which limits their widespread use. By integrating neuro-inspired features into AI, we can create smaller and smarter systems that mimic how our brains process information, improving their effectiveness in recognizing patterns and making decisions. This leads to more efficient and effective AI applications.

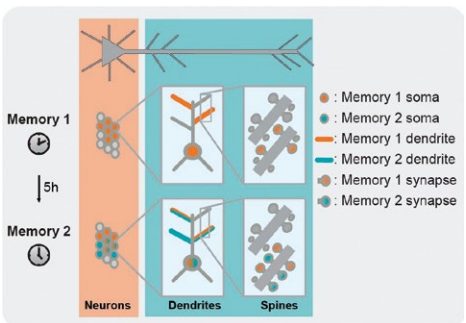
Work carried out by Dr. Spyridon Chavlis, a postdoctoral researcher at IMBB, and supervised by Dr. Panayiota Poirazi proposed a novel architecture for artificial neurons that incorporate different features of biological dendrites, and tested it in various image recognition scenarios.

Dendrites are the branched extensions of nerve cells that resemble tree branches. Their main function is to receive information from other neurons and transmit it to the cell body. For many years, the role of dendrites in information processing was unclear, but recent studies have revealed that they can perform complex calculations independently of the main neuron. Additionally, dendrites are essential for the brain's plasticity, which is its ability to adapt to changing environments.

The findings show that these dendritic ANNs are more resistant to overfitting and can match or exceed the performance of traditional ANNs while using much fewer resources, namely trainable parameters and learning steps. This improvement arises from a unique learning approach, whereby multiple nodes in the network contribute to the encoding of different categories. This is contrary to traditional ANNs, whereby most nodes are category-specific. Overall, this research suggests that incorporating dendritic features can make ANNs smarter and more efficient.

Chavlis, S. and Poirazi, P. (2025) ***Nature Communications*** *16:943*

Dendritic plasticity links memories across time



Scientists have long puzzled over how our brains connect memories of events that happen close together in time. A new collaborative study between research teams at the IMBB, UCLA and Ohio State University shows that the answer lies in the tiny branches of neurons, called dendrites.

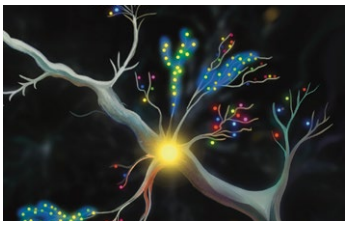
The researchers used advanced brain imaging to monitor dendrites in the retrosplenial cortex, a brain region important for memory, as mice formed memories of different contexts. They found that dendrites are divided into compartments, and each compartment can undergo changes (plasticity) independently. When two experiences occurred close in time, the same dendritic compartments were modified, effectively "linking" the memories. When experiences were farther apart, different compartments were used, keeping the memories separate.

To test whether this mechanism could explain memory linking more broadly, IMBB researcher Dr. George Kastellakis, under the supervision of Dr. Panayiota Poirazi, built a computational model of dendritic plasticity. This model simulated how connections within dendritic compartments are strengthened or weakened depending on when events occur. The simulations showed that overlapping use of the same dendritic compartments naturally produces linked memories, while separate compartments keep memories distinct. This is done through the co-strengthening of groups (clusters) of synapses in common dendrites. In other words, the model confirmed that dendrites act like filing drawers: if two memories are stored in the same drawer, they become connected; if stored in different drawers, they remain independent.

This combination of experiments and modeling provides strong evidence that compartmentalized dendritic plasticity is a key biological mechanism for linking memories across time. The work also highlights how computational approaches can validate and extend biological findings, offering a bridge between microscopic brain processes and the way we experience memory in everyday life. Understanding these mechanisms could eventually help in designing therapies for memory-related disorders, such as PTSD, where unwanted links between memories occur.

Sehgal, M., et al. (2025) ***Nature Neuroscience*** *28, pages 602–615*

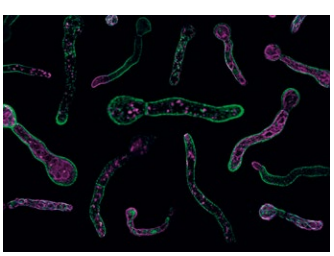
Activity-dependent K^+ hotspots selectively boost the dendritic excitability of neurons, acting as 'volume knobs'



In the publication "Local changes in potassium ions modulate dendritic integration", Dr. Athanasia Papoutsi along with collaborators from the University of Copenhagen in Denmark and University of Bordeaux in France, bring forward the novel concept that local, activity-dependent changes in the extracellular potassium concentration ($[K^+]_o$) create dendritic '$[K^+]_o$ hotspots'. Specifically, authors leveraged the advantages of mathematical formalism and biophysical modeling to explore the role of brain state-dependent $[K^+]_o$ changes on the elaborate processing unit of neurons, the dendrites, using visual information processing as a framework of study. Results show that the spatial arrangement of feature-tuned inputs determines the magnitude of activity-dependent $[K^+]_o$ changes in dendrites. These $[K^+]_o$ elevations in turn depolarize E_{K+} which increases the reliability of dendritic spikes and prolongs their duration. Ultimately, these hotspots act as a volume knob by amplifying the gain of neuronal input–output transformations, leading to higher firing rates at the soma. This work is a proof-of-concept of a novel form of plasticity that selectively boosts the activity of repetitively active dendrites, with time scales of the order of several hundreds of milliseconds to seconds, following that of the brain states, while requiring minimal usage of resources. Importantly, results can be generalized to other sensory features, brain regions, or animal species. As chronic cortical $[K^+]_o$ elevation is observed in several neurodegenerative disease models, including Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease, these results further indicate that dysregulation of $[K^+]_o$ may drive neuronal hyperexcitability and potentially neuronal loss in these diseases.

Nordentoft, M.S., et al. (2025) ***PLoS Biol****. 22(12): e3002935*

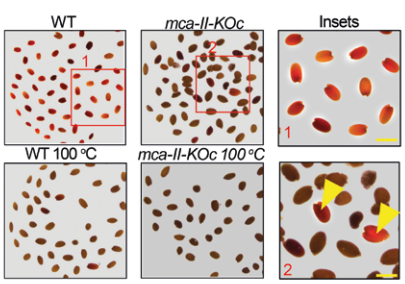
Distinct trafficking routes of polarized and non-polarized membrane cargoes in *Aspergillus nidulans*



Proteins embedded in cell membranes comprise approximately one-third of all proteins in higher organisms (fungi, plants, and animals), collectively known as eukaryotes. The majority of these proteins are associated with the peripheral plasma membrane (PM). Within PM proteins, transporters, channels, and receptors are the most abundant types of polytopic transmembrane proteins, performing essential functions for cell nutrition, detoxification, communication with the environment and other cells, signaling, and stress response. Their significance is underscored by their association with genetic diseases (e.g., cystic fibrosis), various pathologies (e.g., diabetes, cancer, neurotransmission defects), and drug responses (multidrug resistance or sensitivity). As hydrophobic proteins, transporters, channels, and receptors are synthesized on ribosomes attached to the Endoplasmic Reticulum (ER), enabling their newly formed peptides to fold while translocating within the lipid bilayer of the ER. From the ER, these proteins traffic through the Golgi apparatus towards the PM, embedded in secretory vesicles. Vesicles exiting the mature Golgi (or Trans-Golgi Network/TGN) eventually fuse with the PM, from which membrane proteins can also be endocytosed for degradation or recycling, depending on cellular needs. The process of membrane trafficking is driven by small GTPases (Arfs and Rabs), tethers, and SNARE proteins that facilitate membrane fusion, along with the cytoskeleton. Much of our current understanding of the mechanisms and regulation of membrane protein trafficking stems from foundational research conducted in mammalian and plant cells, but particularly from studies in the yeast Saccharomyces cerevisiae (Nobel Prize winners Rothman, Schekman, and Südhof in 2013). However, recent work by George Diallinas, an affiliated researcher at IMBB and Professor in the Department of Biology at the University of Athens, challenges the existing consensus on membrane trafficking. His group has utilized the fungus *Aspergillus nidulans* as a model cell system, developing genetic methods to track the trafficking of various membrane proteins through fluorescence microscopy in living cells. This system was applied to both wild-type and engineered cells where conventional Golgi-dependent trafficking could be genetically inhibited. The results conclusively demonstrated that while essential polarized proteins necessary for growth traffic to the apical PM via conventional secretion, transporters can bypass the Golgi and reach the PM directly. Furthermore, this research reveals that both conventional and this newly identified unconventional trafficking route are established early at the level of cargo partitioning in distinct subdomains of the ER membrane. Thus, this work provides a paradigm shift in our understanding of membrane protein trafficking and may contribute to strategies for combating fungal pathogens, an emerging threat highlighted by the World Health Organization.

Sagia, G.M., et al. (2024) ***eLife*** *13:e103355*

Seed longevity is controlled by metacaspases

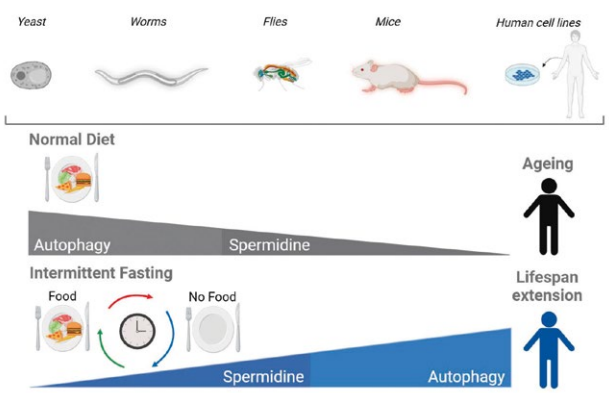


Seeds have an extraordinary ability to survive in a dried, dormant state for years, sometimes even thousands. To pull off this biological feat, they stockpile protective proteins and energy-rich lipids, but the underlying machinery that helps them maintain healthy proteins during this long sleep has remained mysterious. Panagiotis Moschou and his collaborators at IMBB uncovered a key part of this machinery. They found that when all six type-II metacaspase enzymes (MCA-IIs), a special class

of proteolytic enzymes, are disrupted in *Arabidopsis thaliana* seeds, the normal system for managing damaged or misfolded proteins breaks down. As a result, the seeds lose their ability to remain viable over time. A major player in this process is CDC48, a protein that acts like a molecular recycler, clearing faulty proteins from the endoplasmic reticulum (ER). Normally, CDC48 moves between the ER and the seed's lipid droplets thanks to an adaptor protein called PUX10. MCA-IIs fine-tune this movement: they cut PUX10, allowing CDC48 to shuttle back and forth as needed. Without MCA-IIs, PUX10 is not properly processed, CDC48 gets stuck at the lipid droplets, and misfolded proteins build up in the ER. This disrupts both protein quality control and lipid droplet behavior, ultimately shortening seed lifespan. Remarkably, removing PUX10 in MCA-II mutants partially restores CDC48's mobility and rescues seed protein balance, giving the seeds a longer life. In essence, this study uncovered how seeds preserve their proteins and endure the passage of time, one of the secrets behind their astonishing longevity.

Liu, C., et al. (2024) ***Nature Communications*** *15:6748*

A conserved spermidine-autophagy axis underlies the anti-ageing benefits of intermittent fastin



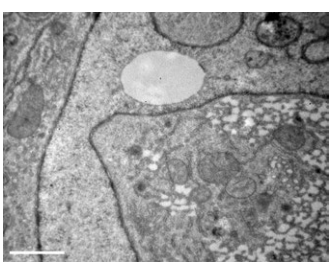
Autophagy is a cellular recycling process involving the lysosomal degradation of dysfunctional or unnecessary components and organelles. Defects in autophagy have been linked to ageing and age-related disorders, such as diabetes, cardiovascular diseases, cancer, and neurodegenerative diseases. Dietary interventions, particularly caloric restriction and intermittent fasting, have been shown to slow ageing and promote longevity, largely by enhancing autophagy.

Spermidine, a naturally occurring polyamine, is known to induce autophagy and extend lifespan. However, its role in intermittent fasting was unclear. Using a range of experimental models, including yeast (*Saccharomyces cerevisiae*), nematodes (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), mice (*Mus musculus*), and human cell lines, IMBB researchers Dr. Ioanna Daskalaki and Dr. Ilias Gkikas, led by Dr. Nektarios Tavernarakis (Professor at the Medical School of the University of Crete), together with collaborators from Prof. Kroemer's team at Université Cité in France and Prof. Madeo's team at the University of Graz in Austria, demonstrated that intermittent fasting increases intracellular spermidine levels. This increase activates autophagy and extends lifespan across species. Conversely, genetic or pharmacological inhibition of endogenous spermidine synthesis abolishes the benefits of intermittent fasting, confirming that spermidine is essential for fasting-induced autophagy and its associated longevity effects. Mechanistically, spermidine exerts these effects by promoting hypusination of the translation regulator eIF5A, leading to autophagy induction.

These findings establish spermidine as a key regulator of the evolutionarily conserved autophagic response to intermittent fasting. They also provide important mechanistic insights into how dietary patterns influence ageing and highlight spermidine-centered pathways as promising targets for interventions aimed at enhancing healthspan and mitigating age-related disease.

Hofer, S.J., Daskalaki, I., et al. (2024) ***Nat Cell Biol****. 26(9):1571–1584*

Endonucleosis mediates internalization of cytoplasm into the nucleus

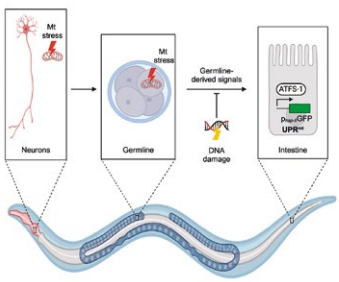


A novel cellular process in which portions of the cytoplasm become internalized into the nucleus and form intranuclear vesicles surrounded by nuclear membrane has been discovered by Ourania Galanopoulou and co-workers in Talianidis Lab. This process, called endonucleosis, occurs in senescent cells and in models with extensive DNA damage, with which the classical DNA repair machinery cannot cope with. The authors have shown that cells can escape extensive genome instability-driven cell death by triggering endoreduplication-mediated hyperploidy, which leads to the enlargement of the nuclei and in increased elasticity of the nuclear membrane, to counterbalance potential mechanical force-driven adverse effects caused by the increased DNA content. Folding of the elastic nuclear membrane towards the nuclear interior and the subsequent membrane closure generates intranuclear vesicles with entrapped cytoplasmic proteins. Hyperploidy and endonucleosis correspond to an unstable and transient cellular state, as the endonucleotic vesicles become smaller and gradually disappear over time with parallel reduction of nuclear size and cellular ploidy. This is achieved via mechanisms involving the segregation of the existing nuclei without mitosis. These processes act towards normalizing the physical characteristics of the surviving cells and their genome, and generate aneuploidy, which together with the activation of oncofetal genes and the parallel accumulation of inflammatory cells, provide a fertile ground for the initiation of cancer.

These features provide support for the concept of the non-genetic function of the genome and chromatin and demonstrate the importance of nuclear envelope plasticity in cellular survival under stress conditions.

Galanopoulou, O., et al. (2024) ***Nature Communications*** *15: 5843*

Germline-derived signals modulate somatic activation of the mitochondrial unfolded protein response



IMBB researchers Dr. Nikolaos Charmpilas (then a postdoctoral researcher at the University of Cologne, Germany), Dr. Aggeliki Sotiriou, and Konstantinos Axarlis, led by Dr. Nektarios Tavernarakis (Professor at the Medical School of the University of Crete) and Dr. Thorsten Hoppe (Professor at the University of Cologne, Germany), have demonstrated that a functional reproductive germline is essential for a robust organismal response to mitochondrial stress.

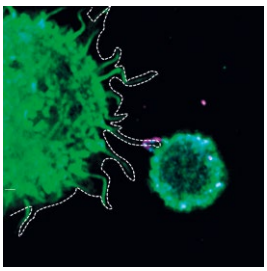
The mitochondrial unfolded protein response (UPRmt) is a key stress response pathway triggered when the mitochondrial protein folding environment is challenged, playing a vital role in maintaining cellular and organismal homeostasis. Using the genetic toolkit of the simple model organism *Caenorhabditis elegans*, the researchers performed extensive genetic analyses and showed that mutant nematodes lacking stem cells, sperm, or oocytes are unable to respond to various genetic or chemical inducers of UPRmt.

Further investigation revealed that reproductive signals, rather than germline stem cells *per se*, are required for somatic UPRmt induction. Thus, somatic cells retain the capacity to activate UPRmt as long as the organism remains reproductively active and capable of producing viable offspring. The study also uncovered the sexually dimorphic nature of UPRmt, demonstrating that male nematodes are inherently UPRmt-nonresponsive. Finally, the authors showed that mitochondrial stress in the immortal germline tissue can activate UPRmt in somatic tissues, establishing a novel germline-to-soma communication paradigm. This mechanism likely acts as a defense strategy to protect the somatic mitochondria of reproductively active adults from stress. The germline maintains UPRmt inducibility in the intestine, which in turn supports the germline through the synthesis and secretion of yolk, thereby providing nutrients to developing embryos.

Collectively, these findings link the organism's response to mitochondrial stress with its reproductive status and highlight that the decline in reproductive capacity is a primary cause of proteostasis collapse during ageing. Understanding the connection between reproductive signals and mitochondrial stress responses may lead to novel interventions to preserve proteome integrity in aging populations and mitigate age-related diseases.

Charmpilas, N., et al. (2024) ***Cell Reports****, Volume 43, Issue 6, 114336*

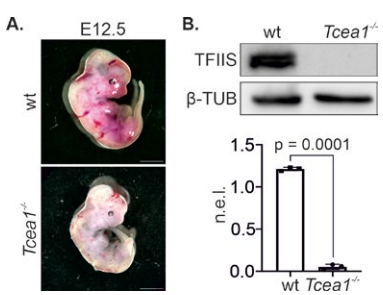
Cancer associated fibroblasts form immune synapses with T regulatory cells, promoting tumor expansion



Using state-of-the-art mouse models and biopsies from cancer patients, the research group led by Panayotis Verginis identified a crucial role of cancer-associated fibroblasts (CAFs) in tumor development, immune evasion and immunotherapy resistance. They demonstrated that α-SMA$^+$ CAFs accumulate in the TME and express immune checkpoint ligands PD-L1 and PD-L2, facilitating the creation of an immunosuppressive tumor stroma. Notably, α-SMA$^+$ CAFs exhibit a tolerogenic phenotype and affect immune cell infiltration and the proteomic contexture of the TME. Moreover, these cells can phagocytose, process and present tumor antigens, instructing movement arrest, activation and proliferation of T regulatory (Treg) cells in an MHC II-dependent manner. Importantly, the data reveal the formation of immune synapses between CAFs and Treg cells, which are reinforced by CAF autophagy and persist despite PD-L1 blockade, indicating that these interactions may constitute a resistance mechanism against immune checkpoint inhibitors. Knocking down autophagy in CAFs led to their inflammatory reprogramming, which attenuated tumor development while reducing Treg cell infiltration into the TME and CAF-mediated Treg activation. Finally, combination of autophagy depletion along with administration of dual immune checkpoint blockade therapy resulted in inhibition of tumor growth and a greater presence of effector T cells in the TME, hinting that targeting of this catabolic pathway in CAFs may ameliorate resistance to immunotherapy. Overall, our findings underscore the therapeutic potential of disrupting CAF-Treg cell interactions and offer new avenues for development of anti-cancer therapies, through combination of CAF-targeted therapies with immune checkpoint inhibition.

Varveri A, et al. (2024) ***Nature Communications*** *15:4988*

Transcription stress at telomeres causes DNA release and senescence



Professor George Garinis and his team at IMBB have uncovered a previously unknown mechanism linking transcription problems to cellular aging. The study shows that when cells lose TFIIS, a factor that helps the transcription machinery move along DNA, the machinery stalls and creates harmful RNA–DNA hybrids called R-loops. These structures accumulate especially at telomeres, the protective ends of chromosomes.

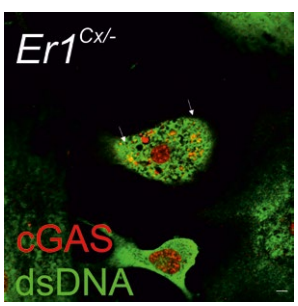
As telomeres become unstable, they shorten, fuse, and break during cell division. The broken pieces of telomeric DNA leak into the cytoplasm, where the cell mistakes them for viral material. This activates a strong innate immune response and pushes the cell into senescence, a permanent shutdown state associated with aging.

Importantly, the research reveals that senescence does not remain confined to individual damaged cells. The leaked telomeric DNA is packaged into extracellular vesicles and released to neighboring cells. When surrounding cells take up these vesicles, they also activate immune pathways and enter senescence. This demonstrates that transcription stress can propagate aging signals across tissues.

The findings describe a direct biological chain connecting transcription blockage, telomere instability, inflammation, and tissue aging — offering new insight into how DNA damage contributes to age-related decline.

Siametis A., et al. (2024) ***Nature Communications*** *15: 4061*

DNA damage in microglia leads to neurodegeneration



A study from the laboratory of Professor George Garinis reveals how DNA damage in microglia, the brain's immune cells, can spark inflammation and accelerate neurodegenerative disease. When microglia lack the DNA repair protein ERCC1, they accumulate persistent DNA breaks. Fragments of DNA spill into the cytoplasm, where the cells interpret them as danger signals. This triggers a powerful antiviral-like immune response and chronic inflammation.

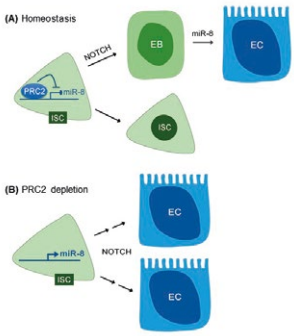
The study shows that microglia then package these DNA fragments into extracellular vesicles and release them into the brain. Neurons take up the vesicles and detect the DNA inside, activating immune pathways that they cannot tolerate. This leads to neuronal stress, death, and early-onset symptoms such as ataxia and tremors in mice.

The research team developed a targeted intervention: vesicles loaded with DNase I, an enzyme that destroys DNA. Delivered into the brain, these therapeutic vesicles remove harmful cytosolic DNA from microglia, suppress inflammation, protect neurons, and delay neurodegeneration.

This work establishes a direct causal link between microglial DNA damage, inflammatory signaling, and neuronal loss — and introduces a promising strategy for treating age-related neurodegenerative disorders.

Arvanitaki, E. S., et al. (2024) ***Proceedings of the National Academy of Sciences*** *121 (17) e2317402121*

Polycomb-mediated silencing of miR-8 is required for maintenance of intestinal stemness in Drosophila melanogaster



Scientists from IMBB and Athens Medical School, led by Zoe Veneti and Aristides Eliopoulos, have made an important contribution to understanding how epigenetic factors regulate adult intestinal stem cells.

Epigenetic factors influence gene expression without altering the DNA sequence. They act by modifying how DNA is packaged and respond to both intrinsic cues (such as aging) and environmental cues (such as nutrition). Adult stem cells are undifferentiated cells that divide throughout life to replenish damaged or lost cells within tissues. In both mammals and insects, intestinal stem cells can generate two main cell types: absorptive cells, which take up nutrients, and endocrine cells, which secrete hormones that communicate the organism's nutritional state.

Using the fruit fly *Drosophila melanogaster*, Veneti and colleagues genetically depleted an epigenetic factor called Enhancer of zeste [E(z)], a protein conserved across plants and animals that silences gene expression by compacting the genetic material. Loss of E(z) in the fly intestine resulted in depletion of intestinal stem cells and an inability to regenerate the gut, ultimately leading to premature death. The researchers demonstrated that this outcome was caused by premature differentiation of stem cells into absorptive cells, which can no longer divide.

Further molecular analysis revealed that, in normal stem cells, many genes promoting absorptive differentiation must remain epigenetically silenced to prevent early loss of stem cell identity. A tiny gene, microRNA-8 (miR-8), was found to play a major role in the stem cell loss observed upon E(z) depletion. Remarkably, simultaneous depletion of both E(z) and miR-8 restored intestinal stem cell numbers.

These findings led to a collaboration with bioinformaticians at Harvard University, who showed that the human homologs of these genes, EZH2 and miR-200, exhibit a similar antagonistic relationship in both healthy and malignant human intestinal tissues. This conservation suggests a fundamental role for these factors in maintaining intestinal health and underscores the power of the fruit fly as a model system for uncovering regulatory mechanisms relevant to human biology.

Veneti, Z., et al. (2024) ***Nature Communications*** *15:1924*

Timeline 2024-2025

2024

JANUARY

Panagiotis Moschou is awarded the prestigious ERC Consolidator Grant

MARCH

The conference on “Exploiting protein evolution for protein engineering” co-organized by IMBB-FORTH and ONRG is held at FORTH

MAY

The Ancient DNA lab of IMBB identifies 18 World War II executed civilians of Adele, Rethymno

Research by George Chamilos group on life-threatening fungal infections is featured in the European “Research Matters” campaign

The Office of Scientific Integrity organized a lecture on bullying in the work place, open to all FORTH

AUGUST

Prestigious H.F.R.I.– SNF grant “Always strive for excellence – Theodoros Papazoglou” is awarded to IMBB researcher Panayiota Poirazi.

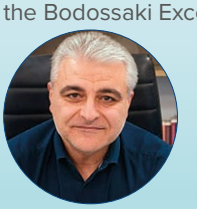
SEPTEMBER

IMBB participates in the “2024 Researcher’s night” event

JUNE

The IMBB & UOC spin-off company "ReNeuroCell Therapeutics" is awarded at the StartSmart SEE Forum

Nektarios Tavernarakis is honored with the Bodossaki Excellence Award

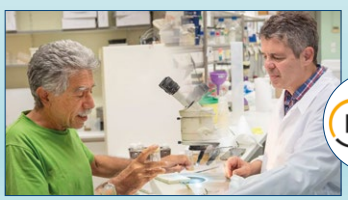


The IMBB Mentoring program hosts EMBO courses on "Fellowship application process" & "Scientific publication process"

JULY

IMBB hosts the international workshop "Vector Control: Insecticides and Beyond"

Christos Delidakis and John Vontas are elected members of the European Organization for Molecular Biology (EMBO)



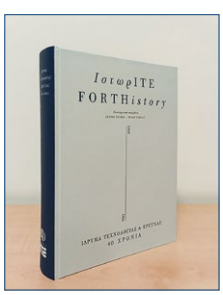
OCTOBER

Electra Gizeli leads the EU-funded Center of Excellence "DxHub" for research on novel solutions for the detection of infectious diseases.

DECEMBER

Vontas group receives a grant from Gates Foundation to develop innovative insecticides for the control of the malaria mosquitos

"FORTHistory": A Commemorative Volume for the 40th Anniversary of FORTH is published.



2025

JANUARY

Daphne Bazopoulou & Ioanna Keklikoglou, Assistant Professors of the Department of Biology, University of Crete join IMBB as collaborating faculty

Nektarios Tavernarakis is elected President of the European Molecular Biology Conference (EMBC)

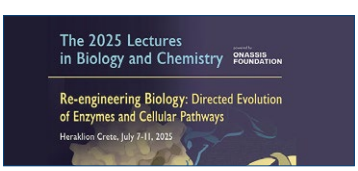
FEBRUARY

"Res Tick", an EU-funded project on studying ticks as vectors of pathogens, is coordinated by IMBB researcher Michail Kotsyfaki)

IMBB researchers participate in the EU-funded project INCLUDE: "Advancing Intersectional Gender Equality in Biomedical Research and Innovation

JULY

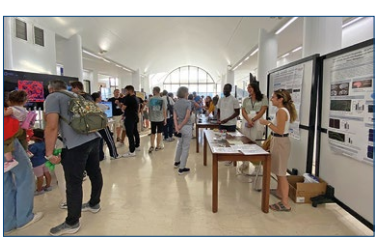
IMBB-FORTH hosts the 2025 Onassis Lecture in Biology & Chemistry



SEPTEMBER

IMBB-FORTH hosts the FENS KAVLI network scientific symposium 2025

IMBB participates in the "Researcher's Night 2025" event



George Garinis in the 'CONTACT POINT": public discussions organized by FORTH outreach activities

MARCH

Nicholas Katsanis, co-founder of Galatea Bio and Antithesis Therapeutics, joins IMBB as adjunct faculty

APRIL

Michail Kotsyfakis is awarded a prestigious HFSP Research Grant for studying Tick-Virus Dynamics

MAY

IMBB-FORTH co-organizes the EMBO International Neuroscience Conference entitled “Cell Biology of the Nervous system”

Tassos Pavlopoulos represents IMBB in the “Rock your science” Science Vision Contest during the EU-LIFE community meeting in Brno, Czechia

OCTOBER

New researcher Eirini Skourtanioti is elected

NOVEMBER

Nektarios Tavernarakis Receives Honorary Doctorate from Ionian University

IMBB Postdocs and PhD students organize the first “Junior Scientists Retreat”

DECEMBER

Emeritus researcher Domna Karagogeos receives the Academy of Athens Award in the field of Multiple Sclerosis

IMBB Procedures

IMBB Procedures

A short note on Mentoring

Note on the Mentoring & Career Track Scheme (MCTS)

The Mentoring and Career Track Scheme (MCTS) is an IMBB initiative designed to support early-stage researchers, with particular emphasis on postdoctoral fellows and PhD candidates approaching completion of their studies, as they consider their next professional steps within or beyond academia.

Over the past two years, the scheme has expanded significantly, offering a broad portfolio of dedicated seminars delivered by life science professionals with distinguished international careers across diverse sectors. Ten invited speakers from academia and industry — including professors leading renowned laboratories in Europe and the United States, young PIs and ERC grant holders, scientific management consultants, CEOs and company founders, as well as professional career advisors — shared their career trajectories and perspectives in engaging, in-person seminars. These events provided practical insights, thoughtful reflections, and valuable lessons learned, while fostering open and stimulating discussions with IMBB researchers. The strong participation and active engagement of our community reflect the value and appreciation of this initiative.

In addition to the seminar series, IMBB hosted two full-day EMBO courses focused on communicating research findings effectively and preparing competitive fellowship applications. Sponsored jointly by EMBO and IMBB, these courses were offered to all early-stage researchers and provided hands-on training in essential professional skills.

The successful organization of these activities was made possible through the continuous commitment of the MCTS Committee members — Manolis Froudarakis, Rodanthi Lasithiotaki, Tassos Pavlopoulos, Kiki Sidiropoulou, Eva Zacharioudaki — whose dedication to mentoring and professional development continues to strengthen support for early-stage researchers.

Finally, it would be remiss not to acknowledge the first IMBB Junior Scientists Retreat, an initiative of the IMBB PhD and Postdoctoral Committee. This two-day event, held at IMBB-FORTH, brought together junior scientists for presentations, poster sessions, and the exchange of scientific ideas in a highly successful and collegial setting.

As the MCTS approaches its fifth year in 2026, the scheme has evolved into a structured and integral component of early-stage researchers' development at IMBB. Through seminars, workshops, and community-building initiatives, the scheme complements scientific training within and beyond the laboratory and remains committed to preparing researchers for diverse and successful career paths.

Electra Gizeli

Head of MCTS Committee, 2024–2025

IMBB-Gender Equality Group (IGEG)

IMBB-FORTH is actively fostering a working environment in which all individuals are treated equally, with decency, respect and fairness, 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. Members of the IMBB-Gender Equality Group (IGEG) are **Dr. Maria Markaki, Dr. Athanasia Papoutsi and Dr. Alexandros Pittis**. The IGEC serves as the first contact point for IMBB personnel who require more information about these issues, wish to contribute new ideas for additional actions, or need advice for reporting complaints. In 2024, IGEC participated in the successful HORIZON-WIDERA proposal INCLUDE (implementation period: 2025-2026). The INCLUDE core team is complemented by Dr. Ioannis Talianidis and Ms. Sofia Kapeloni. The INCLUDE Project aims to promote gender equality and intersectionality in biomedical research and higher education institutions across Europe through inclusive, evidence-based and participatory actions. The project brings together research institutes and universities, with a strong emphasis on widening countries, to address gender inequalities in research careers, leadership, and scientific content. At IMBB, the project has already led to concrete actions in 2025: an internal assessment was carried out, including interviews with IMBB members and analysis of FORTH's GEP, to identify existing gaps, needs, and good practices. Following approval of the IMBB Scientific Council, a dedicated INCLUDE Working Group was established, bringing together a diverse group of members committed to promoting equity and inclusion across IMBB career stages. The Working Group has been actively involved in the co-design and implementation of pilot actions, awareness-raising activities, and internal discussions on gender, intersectionality, and inclusion in biomedical research. IMBB was also responsible for one of the project's Thematic Hubs: *Sex and Gender in the contents of Biomedical Research*. Through a series of interactive sessions, IMBB has contributed to collective learning and reflection on how sex, gender and intersectionality can be meaningfully integrated into research design, methods, and scientific knowledge production. At the same time, IMBB has participated in capacity-building activities, including Train-the-Trainers sessions, study visits and informative sessions addressing topics such as gender+ terminology, gender-based violence in academia and practical ways to integrate the gender dimension in research content. Project activities have also been linked to public engagement initiatives, such as Researchers' Night, enhancing visibility and dialogue around gender equality and diverse needs within the research community.

IGEG is linked to:

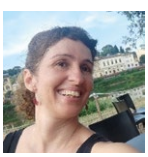
FORTH's Gender Equality and anti-Discrimination Committee

EU-Life Gender Equality Working Group

INCLUDE project

The IMBB-Gender Equality Group (IGEG)

Maria Markaki



Athanasia Papoutsi

Alexandros Pittis

Activities of the INCLUDE Working Group

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 and related good practices in the context of the Research Environment such as Training and Supervision, Research Procedures, Safeguarding, and Publication and Dissemination. Another 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. In 2024 the Office of Scientific Integrity organized a lecture on bullying in the work place.

Members of the Office of Scientific Integrity:

George Mavrothalassitis

Maria Monastirioti

Irini Stratidaki

Zacharenia Vlata

Outreach Activities

Outreach Activities

Researcher's Night at IMBB

Every year IMBB and FORTH open their doors to everyone who is interested to learn more about the science and research that we do. Researcher's Night has become a huge success with more than 2000 visitors each year. Here, IMBB laboratories present their research and scientific progress in a fun and easy to understand way. Visitors are invited to participate in scientific experiments themselves and explore the methods that are used to answer important scientific questions. The interaction of young researchers with the public at Researcher's Night is a great inspiration for their continued dedication to science. The event is funded by the European Union and is held with the support of the Region of Crete and the Regional Development Fund of Crete.

Podcast "επικοινωνvITE": Yiota Poirazi "The brain: The smartest system in the universe"

In the fourth episode of the podcast series "επικοινωνvITE" Dr Yiota Poirazi, Research Director at IMBB, talked to Anthi Strataki about the complex functions of the brain. The enormous progress in neuroscience already surpasses science fiction as Dr Poirazi explained. She talked about how dendrites processes information like small computers, and how the hippocampus of the brain transforms our experiences into memories. Furthermore, she also explained how the architecture of the brain inspires artificial intelligence.

The podcast series "επικοινωνvITE" is a new initiative from FORTH featuring an original series of conversations and is part of the "FORTHreach" initiative. The aim of the podcast series is to bring science closer to everyday life. Through accessible talks and activities by FORTH scientists, it highlights research discoveries and explores how scientific knowledge connects with the values that shape our society.

The series is available on the YouTube channel of FORTH in the Greek language.

CONTACT POINT: "And They Lived Happily Ever After: Ageing and Well-being"

The second event of the series CONTACT PONT, entitled "And They Lived Happily Ever After: Ageing and Well-being", took place at FORTH's new Science and Cultural Center in Heraklion, Crete. It featured George Garinis, Collaborating Faculty Member at IMBB and Professor of Genetics at the University of Crete and the author Sophia Madouvalou. Together they explored the common ground between scientific research, storytelling, and the human experience around the subject of Ageing, which was approached not only as a biological process but also as a human experience.

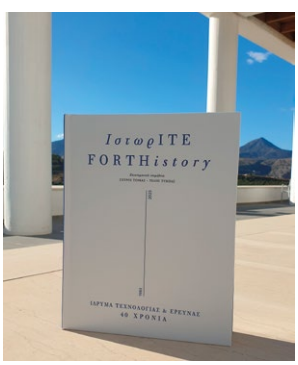
The activities of "Contact Point" at FORTH is an original series of public discussions, each featuring a FORTH scientist and a distinguished artist. "Contact Point" brings Science and Culture into Creative Dialogue, fostering open and meaningful communication of science through art.

IMBB in the Innovation Exhibition “Innodays 2025” Crete of Knowledge and Production

The Innovation Exhibition InnoDays took place at November 28–30 November 2025 at the International Exhibition Center of Crete. The event was organized by the Region of Crete, implemented by the Innovation Business Observatory (IBO) of Crete Region and was held under the auspices of the Ministry of Development and the General Secretariat for Research and Innovation. IMBB participated with researcher Konstantinos Stratakis who gave a talk at the opening ceremony entitled “Precision Medicine, Genetics & Innovation: Today and in the Future” and IMBB Director John Vontas who participated in the panel discussing “Strategic Collaboration Between ELGO-DIMITRA & FORTH”.

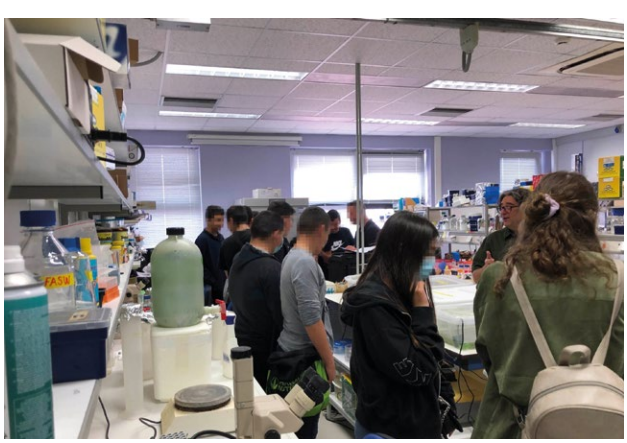
IMBB also participated with the exhibits “Bio-based insecticides for controlling harmful insects such as olive fruit flies and disease-carrying mosquitoes” from the group of John Vontas. “Innovative, low-cost, rapid Salmonella detection method using gold nanoparticles” was presented by Electra Gizeli laboratory, while the exhibit by the group of Dimitris Tzeranis was titled “Precision Pharmaceutical Application Systems and Medical Robotics Utilizing Biomaterials for wound healing and regenerative medicine, with applications in central nervous system therapies”. Another IMBB exhibit was “Portable 3D-printed device for detecting arthropod-borne pathogens”, the result of a collaboration between Michail Kotsyfakis lab with FORTH spin-off BIOPIX-T.

FORTHistory book



The first 40 years of FORTH history was published in 2024. The book FORTHistory («ΙστωρΙΤΕ») (in Greek) provides a scientific analysis of FORTH and its role in Greek science during the last 40 years. The history of IMBB is covered in great detail, showing its development from a few laboratories to the successful research Institute of today. The text is complemented by many historic photos. It is published by Crete University Press.

IMBB participates in FORTH program of school visits



IMBB actively participates in the school visit program of FORTH, reflecting the Institute's commitment to inspiring the younger generation to pursue careers in the Life Sciences and to familiarizing students with a modern research environment. During the 2024–2025 period, IMBB welcomed more than 300 high school students to its premises, primarily from Crete as well as other regions of Greece. The visits were coordinated and hosted by IMBB Researcher Dr Anastasios (Tassos) Pavlopoulos, who guided pupils through several research units of the Institute. Students visited the Developmental Morphogenesis Laboratory, the Genomics Facility (presented by Ms Irini Stratidaki), the Fly Facility (presented by Prof. Christos Delidakis and Mr Ioannis Livadaras), as well as other laboratories, gaining first-hand exposure to contemporary biological research and state-of-the-art research infrastructures.

DxHub Youth for Diagnostics Citizen Science Programme

DxHub is an Excellence Hub, funded by Horizon Europe. DxHub aims to transform the future of diagnostics, by combining fundamental research with technological innovations to create molecular diagnostic solutions at the point of case that will have a real impact to everyday life. To achieve this, DxHub is creating a quadruple helix alliance, linking academia with businesses, policy makers and societal actors from Greece and Portugal. One of the main goals of the DxHub project is to engage local communities and raise awareness about the need for point-of-care (POC) diagnostic and surveillance solutions for the early detection and mitigation of pathogens, contributing to disease prevention. Aligned with this goal, three Citizen Science Programmes have been implemented in Greece and Portugal. "Youth for Diagnostics", initiated in September 2025, is a two-year STEAM-based initiative that engages high school students from 18 schools of the Heraklion prefecture, in real-world water diagnostics through citizen science and it is the first citizen science project in Crete to engage high school students. Students will gain hands-on experience by participating in real scientific efforts, assisting researchers in answering questions related to the environment and public health issues, while equipped with knowledge and skills for water microbiology and the development and use of field-deployable diagnostic technologies. The ultimate goal of the program is the creation of a diagnostic tool for detecting microorganisms in water by the students. DxHub is coordinated by Professor Electra Gizeli, University of Crete, and collaborating faculty member at IMBB.

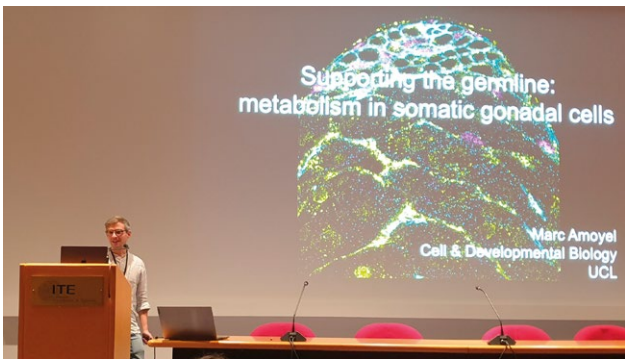
Thessaloniki International Fair

IMBB participates with exhibitions at the annual Thessaloniki International Fair showcasing a selection of the research projects of the Institute. The group of Professor Dimitris Tzeranis presented their novel approaches to therapy of neurodegenerative diseases. The group is developing novel systems and devices around biologically-active biomaterials by integrating engineering, materials science, optics, and biology. EDIMO, the Greek Network in Molecular Oncology, explained how new approaches to treat patients with cancer with personalized plans for therapy will improve patient care and disease outcome. The laboratory of Professor John Vontas showed how novel methods are being developed for protection against mosquitoes and insects of agricultural importance. Novel diagnostic methods for detection of microorganisms and pathogens were presented by the group of Professor Electra Gizeli, while Finally, Dr Michail Kotsyfakis reported on a novel application developed in collaboration with the IMBB startup BIOPIX-T for diagnostics of tick-borne disease agents.

The Onassis Foundation Science Lecture Series 2025

The Onassis Foundation Science Lectures are hosted at FORTH. In 2025 the topic of the lectures was Biology, with the title “Redesigning Biology: Directed Evolution of Enzymes and Cellular Pathways”, one of the most dynamic and rapidly evolving fields of modern biology — where laboratory evolution and synthetic biology intersect with artificial intelligence and cutting-edge technology. The lectures bring together distinguished international scientists who present front-line research and applications. The lectures series aim to further educate and promote young, talented scientists, at the pre- and post-graduate level as well as postdoctoral scientists in the field of physical and life sciences. The keynote Speaker of this year’s lectures, Prof. Frances Arnold, Nobel Laureate in Chemistry (2018), also gave a public lecture entitled: “Innovation by Evolution”. Frances Arnold is a highly distinguished figure in the fields of Science and Technology. In addition to receiving the Nobel Prize in Chemistry, she is the first female scientist to ever be elected as a Fellow of all three National Academies of the USA (Engineering, Medicine, Science).

IMBB Junior Scientists Retreat



IMBB hosted the Junior Scientists Retreat, a two-day event dedicated to scientific exchange, collaboration, and the professional development of early-career researchers with an interest in molecular biology. The retreat featured keynote lectures by Vilaiwan Fernandes, who presented her research on “*Integration of distinct signalling modalities to achieve single-cell patterning resolution*” in the *Drosophila* brain, and Marc Amoyel, who discussed how metabolism in somatic gonadal cells supports germline development in the *Drosophila* testis, with the latter session sponsored by HE-Twinning SCENTINEL_EU.

PhD candidates and postdoctoral researchers from different institutions in Heraklion delivered outstanding scientific talks, highlighting the depth and diversity of research at the institute, while dynamic poster sessions fostered lively discussions and new collaborations.

The retreat also included an engaging discussion with Spyros Artavanis-Tsakonas on the research landscape in Greece and concluded with social activities, including a treasure hunt and an evening of wine tasting, music, and dancing, providing participants with an opportunity to strengthen connections and celebrate the success of the event.

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. David Van Vactor

Harvard Medical School,
Boston, USA

Dr. Tomas Kirchhausen

Boston Children's Hospital,
Boston, USA

Dr. Daniel Louvard

Institut Curie, Paris, France

Dr. Irene Papatheodorou

Earlham Institute,
Norwich, UK

Dr. Patricia Gaspar

School of Neurosciences,
Paris, France

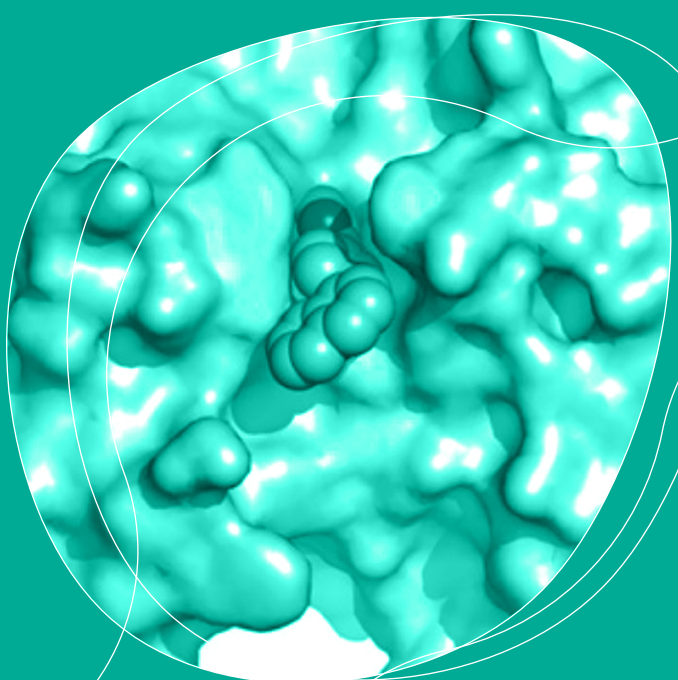
Dr. Angeliki Louvi

Yale School of Medicine, New Haven, USA

Dr. Nikos Hatzakis

University of Copenhagen,
Copenhagen, Denmark

Structural Biology, Biophysics- Nanobiotechnology



Electra Gizeli

Professor / Biology Department, University of Crete –Collaborating Faculty Member

BIOSENSORS

GROUP MEMBERS

Principal Staff Scientist: Achilleas Tsortos
Postdoctoral Researchers: Konstantina Alexaki, Dimitra Chronaki, Anastasia Galanopoulou, Martha Valiadi, Despoina Varamogianni, Fred Verret
Research Assistants: George Karolidis (MSc), Maria Megariti (MSc), Isabella Papadopoulou (MSc), Eugenia Papastefanaki (MSc), George Perakis (MSc), Vaia Tsiakalou (MSc), Zenia Viskadouraki (MSc), Christos Chatzaras
PhD students: Katherine Hartle-Mougiou, Stelios Grammatikos
MSc students: George Kousis, Yannis Markopoulos
Management & Dissemination: Dr Anjie Kolokousi, Chara Mavromati (MSc)
Undergraduate thesis students: Triantafyllia Gora, Orestis Kokolakis, Natalia Kontaxi, Aristea Michalopoulou, Iris Panagopoulou, Vasia Triantafylla
Visiting Scientists: Dr Kaouther Ayouni (Inst. Pasteur, Tunisia), Dr Wahida Bhuyian (National Oceanography Centre, UK), Dr. Augusto Juste Dolz (Universidad Politécnica de Valencia), Dr Luca Morelli (Southern Denmark University)

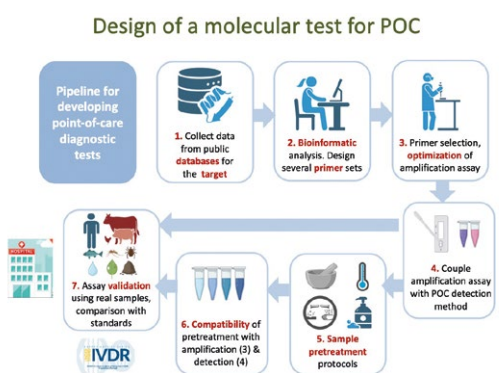
Summary

Our mission is to make healthcare accessible to all, improve global health and contribute in the reduction of sickness and mortality through the delivery of effective interventions in diagnostics and environmental monitoring. To meet this goal, we have pioneered novel solutions for diagnostics at the point-of-care (POC) for the detection of emerging pathogens. Isothermal amplification methods, *i.e.*, the loop mediated isothermal amplification (LAMP) or recombinase polymerase amplification (RPA), are used for target amplification outside a centralized lab combined with nanoparticles or lateral flow strip technologies for detection. We also develop portable, affordable and simple to operate devices, fabricated in our lab using 3D-printing, for quantitative interpretation of our results.

Current aims

We continue our multidisciplinary work in the following main areas:

- **Advancements in diagnostics and nucleic acids monitoring within One-Health.** We are applying our methodologies to the detection of Arbo-, influenza and Corona viruses in human samples as well as genetic mutations. In addition, monitoring the environment, i.e., the sea, plants and insects, is part of our work, for the detection of harmful algae, toxins, plantborne pathogens, and vector borne diseases.
- **Nano-biotechnology**. We are investigating the use of novel green-synthesized nano-probes for the detection of nucleic acids in amplification reactions. Within this context, we investigate their compatibility with polymerase-enzymes, deoxy-nucleotides (dNTPs) and LAMP buffer-reagents.
- **Translational activities**. We continue our efforts to identify lab-innovations with impact in the society and communicate our results to relevant stakeholders always with respect to global challenges within healthcare and One-Health.



Progress in 2024-2025

i) We developed a novel *in silico* pipeline for primers design enabling the (1) identification of conserved regions within big heterogeneous genomic datasets (2) primers design & optimization and (3) testing for specificity and inclusivity. (Funded by: EU UniHealth)
ii) A strategy for the rapid design of diagnostic tests of emerging pathogens for pandemic preparedness was demonstrated in a clinical setting for SARS-CoV-2, MERS, Influenza A (H1N1, H1N3, H5N1), Zika and West Nile (lineage 1 and 2). West Nile and Zika assays are also applied to One Health, *e.g.*, in humans and mosquitoes (see Figure). (UniHealth)
iii) First demonstration of a molecular rapid test for HIV and sickle cell disease at the POC using RPA and lateral-flow-strip (LFS) for detection. (EU Free@POC; FORTH)
iv) Three new patented detection methodologies include a LFS reader compatible with RPA, gold nano-probes for colorimetric and fluorescent detection combined with LAMP and a portable acoustic biosensing platform combined with paper fluidics for immune-sensing. (EU: UniHealth, AquaBioSens)
v) *In situ* marine analyzers and portable biosensing technologies were developed and implemented for autonomous on-site monitoring of invasive species, pollutants, pathogens, and toxins. This work aims to make water-quality monitoring faster, smarter, and accessible to all. (EU: AquaBioSens, TechOcean, UniHealth).

Other activities

- PhD student Stelios Grammatikos recipient of the HFRI and Maria M. Manassaki PhD Scholarship award
- Anjie Kolokousi organizer of citizens-engaging activities (“School Living Lab”, “Youth driven point of care diagnostics” and “Mosquitoes watch”) within Excellence Hub project coordinated by Electra Gizeli (DxHub)
- Electra Gizeli awarded a Fulbright Exchange Visitor Fellowship to Harvard Medical School

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

Publications:

Ntimtsas A and Gizeli E (2024) Portable Surface Acoustic Wave device platform coupled with a paper-based capillary fluidics for real-time biosensing applications. **Sensors & Actuators A: Physical** 378: 115814

Megariti M, et al. (2024) Rapid real-time quantitative colorimetric LAMP methodology for field detection of Verticillium dahliae in crude olive-plant samples. **Plant Methods** 20, Article number: 139

Hartle-Mougiou K, et al. (2024) Development of a quantitative colorimetric LAMP assay for fast and targeted molecular detection of the invasive lionfish Pterois miles from environmental DNA. **Frontiers in Marine Science** DOI 10.3389/fmars.2024.1358793

Giorgos Gouridis

Principal Researcher

GROUP MEMBERS

Senior research personnel: Mary Providaki
Postdoctoral researchers: Alexis Molfetas, Eleni Makraki (former)
PhD students: Chara Sarafoglou

DYNAMIC STRUCTURAL BIOLOGY

Summary

Our group aims to decode how protein machines fold, switch, and evolve by quantifying state occupancies on their energy landscapes. We combine solution single-molecule FRET with HDX-MS, SEC-MALS and structural methods to map allosteric pathways and kinetic checkpoints. A central goal is to identify structural elements that reshape enthalpic–entropic balances, lower barriers, and bias ensembles toward functional states, enabling predictive control of mechanism and specificity. In 2024–2025 we consolidated this pipeline into QC-hardened SOPs for reuse.

Our 2024–2025 work highlights protein modularity: conserved cores acquire small secondary-structure 'embellishments' that rewire allosteric networks and resolve evolutionary trade-offs. We posted two preprints describing (i) NEXT-FRET, a solution smFRET framework that resolves short-lived folding intermediates, and (ii) thermodynamic affinity–efficiency trade-offs in bilobed proteins under resource constraints. These principles now guide our Ras and nuclear-receptor programmes.

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. We pursue state-resolved biophysics on three protein classes: (i) bacterial bilobed proteins (SBPs and related scaffolds) to derive quantitative rules for allostery, evolvability and folding; (ii) nuclear-receptor switches (Nurr1, RXRα) where tertiary/quaternary dynamics control transcription and provide tractable druggable states; and (iii) Ras signaling proteins, whose dynamic oligomerization and nanoclustering underlie ~30% of cancers. Across these systems we integrate smFRET, HDX-MS, SEC-MALS, crystallography and modeling, and we translate mechanisms into screening-ready assays (NEXT-FRET/HTS). Key collaborations include Kymatonics/IESL (optics), IACM-Pantazis (analysis), Dömling (medicinal chemistry) and the Talianidis laboratory for organoid validation. Our vision remains to strengthen a unique Greek hub for dynamic structural biology and mechanism-anchored drug discovery. Access to EMBL-Hamburg beamlines and ProFI workflows ensures rapid structure/dynamics cycles, QC, and dissemination through student courses and mini-workshops.

Progress in 2024-2025

I) In 2024–2025 we consolidated our quantitative pipeline and expanded crystallography, SEC-MALS and HDX-MS workflows, enabling state-resolved discovery and translation.

a) We upgraded our solution smFRET microscope and analysis to support NEXT-FRET, enabling automated trajectory classification under non-equilibrium conditions.

b) We integrated HDX-MS with SEC-MALS and QC, producing state-dependent protection maps for key targets.

c) We expanded modeling: statistical coupling analysis and MD/AI interpretation now connect smFRET/HDX-MS observables to allosteric networks. In parallel, we solved high-quality crystal structures capturing multiple open/closed and engineered states in SBPs and Ras.

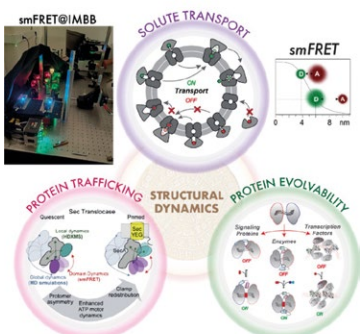
II) We elucidated the role of structural dynamics in:

a) Folding checkpoints: NEXT-FRET resolved an on-pathway closed intermediate and showed how signal peptides and chaperones bias trajectories, linking proteostasis factors to landscape reshaping under native, solution conditions.

b) Allosteric evolution: using SCA, smFRET, HDX-MS and calorimetry we mapped independent allosteric components and quantified an affinity–efficiency trade-off, rationalizing niche-dependent selection under resource constraints across phylogenies. This activity is further strengthened by an HFRI-funded delocalized fellowship (D. Kyprianidi; main supervisor P. Pavlidis, UoC Biology; co-supervised in our lab) focused on advancing and validating our SCA framework across datasets.

c) Plasticity and conditional neutrality: we combined neutral mutations with controlled changes in a C-terminal helix to switch or abolish SBP specificity, tuning open/closed equilibria over ~106 affinity range. The framework directly informs engineering and druggability by targeting allosteric modules.

III) We initiated translational lines in close collaboration with SMEs SyNoesis Therapeutics (Cyprus) and Argo Therapeutics (Switzerland): SEC-MALS provided in vitro evidence for higher-order Ras assemblies and for RXRα–Nurr1 complex remodeling by ligands, establishing mechanistic assays that will connect conformational states to cellular readouts and organoids.



Other activities

- Two trainees completed theses and moved on to next steps (ETH Zurich postdoc; CREA-VE PhD), while new MSc/BSc students entered the pipeline.
- Delivered invited Onassis Foundation Lectures (2025)
- Dr Gouridis co-supervises two Medical School doctoral theses, ensuring harmonised biobanking, SOPs and clinically anchored assay development (PROFI activities).

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

Publications

Sarafoglou C, et al. (2025) NEXT-FRET: A solution-based smFRET platform to resolve folding intermediates under native conditions. **bioRxiv**, doi:10.1101/2025.07.30.666321. Under review (PNAS); solution smFRET plus

Muthahari Y, et al. (2025) Allosteric evolution under resource constraints: thermodynamic trade-offs between affinity and efficiency. **bioRxiv**, doi:10.1101/2025.10.08.680613. Links ecology to allosteric components mapped by SCA.

Michael Kokkinidis

Professor Emeritus / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Senior Research Technicians: Dina Kotsyfaki (until March 2024), Mary Providaki (until the end of 2024)

PROTEIN STRUCTURE/CRYSTALLOGRAPHY

Summary

Building on our earlier structural studies of highly regular α-helical proteins, we have expanded our understanding of protein folding and sequence–structure relationships into remote regions of protein sequence space that are sparsely populated by natural proteins. This expanded conceptual framework is based on the reversal of protein sequences (retro-proteins) and provides a robust foundation for the rational design and engineering of novel proteins and exotic bio-inspired materials, with promising applications in health and materials science.

We have further refined our discovery of the novel autocatalytic hydroxylation mechanism in peptidoglycan N-acetylglucosamine (GlcNAc) deacetylases from pathogenic bacteria, including Bacillus cereus and Bacillus anthracis. This reaction uniquely targets the Cα atom of proline, representing the smallest post-translational modification identified to date. Through combined biochemical and structural analyses, we elucidated the chemical basis of this unusual autocatalytic process, which may have broad implications beyond bacterial pathogenicity, e.g. cancer and neurodegenerative disorders. We also investigated the structural determinants governing inhibition of the hydroxylation reaction by specific small-molecule inhibitors. In parallel, we analyzed the topology of the conserved catalytic NodB domain in carbohydrate esterase family 4 (CE4) deacetylases to relate key structural features of the fold to functional properties such as catalysis and self-hydroxylation.

In collaboration with the Medical School of the University of Crete, we additionally pursued a structural analysis of the human brain enzyme glutamate dehydrogenase 2 (GDH2), with the aim of understanding its evolutionary adaptations in humans and modern apes.

Current aims

- To exploit amino acid sequence reversal as a powerful tool for probing sequence–structure relationships across vast and understudied regions of protein sequence space.
- To elucidate the mechanism, extent, and biological consequences of autocatalytic Cα hydroxylation, including its structural and functional impact, its evolutionary role in enzymes of the CE4 family, including pseudo enzymes, and potential links to human disease (e.g. proline or glycine Cα hydroxylation and bacterial pathogenicity, cancer or neurodegenerative disorders).
- To perform comparative structure–function analyses of GDH2 from humans and great apes, with the dual goals of elucidating aspects of human brain evolution and identifying new opportunities for drug discovery in cancer and neurodegenerative diseases.

Progress in 2024-2025

i) **Sequence reversal and protein folding**

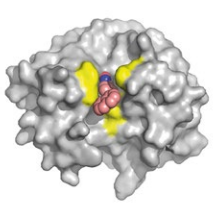
In collaboration with the Department of Mathematics and Applied Mathematics at the University of Crete, we further explored amino acid sequence reversal as both a protein design strategy and a tool for protein-folding analysis. Using atomistic molecular dynamics (MD) simulations, we probed remote regions of protein sequence space with engineered α-helical bundle retro-proteins. The structurally simple wild-type Rop (wtRop) protein served as an ideal model system. The computational studies were complemented by experimental characterization of two reversed variants of wtRop: a fully reversed sequence (rRop) and a partially reversed sequence (prRop). Simulations revealed disruption of the native α-helical architecture in both retro-proteins, the emergence of additional secondary structural elements, and reduced structural stability relative to wtRop. In dimeric models, corruption of the hydrophobic core was also observed. These findings are consistent with circular dichroism (CD) spectroscopy of prRop, which indicates an unstable yet highly α-helical protein.

ii) **Autocatalytic Cα hydroxylation in CE4 enzymes**

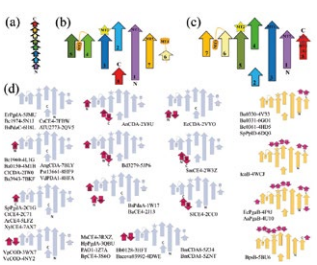
Beyond proline Cα hydroxylation, we analyzed autocatalytic hydroxylation of glycine residues, revealing the occurrence of both single and double hydroxylation events. Self-hydroxylation mechanisms were investigated across multiple members of the CE4 family, including pseudoenzymes that have evolved altered or diminished catalytic activity. The highest frequency of hydroxylation events is associated with the metal-binding region of the enzyme, where we identified a putative hydroxylation triad. The precise chemical and enzymatic nature of protein self-hydroxylation remains under active investigation. Crystallographic studies (PDB ID: 5O6Y) further provided a structural basis for the rational design of inhibitors targeting the catalytic/ hydroxylation reaction in CE4 deacetylases.

iii) **Evolutionary adaptations of GDH2**

Based on crystallographic analyses of human GDH2, we developed a structure-based model describing the evolutionary adaptations of this key metabolic enzyme in modern apes and humans over the past 23 million years.



Crystal structure of the deacetylase BC1960 from *B.cereus*, in complex with the deacetylase inhibitor N-hydroxy-4-(naphthalene-1-yl) benzamide



Topological analysis of the NodB architecture. For the sake of simplicity, only the β-strand arrangement is shown.

Other activities

- Guest Editor Intl. J. Mol. Sci.

Web page www.imbb.forth.gr/kokkinidis

Publications

Tsakiri D, et al. (2025) Subcellular targets and recognition mechanism of *Ralstonia solanacearum* effector RipE1. **iScience** 28(5):112307

Molfetas AS, et al. (2024) Variations of the NodB Architecture Are Attuned to Functional Specificities into and beyond the Carbohydrate Esterase Family 4. **Biomolecules** 14(3):325

Arnittali M, et al. (2024) Structure of amino acid sequence-reversed wtRop protein: insights from atomistic molecular dynamics simulations. **J Biomol Struct Dyn**. 42(19):9842-9856

Dimitrios Tzeranis

Assistant Professor / Department of Materials Science and Technology, University of Crete – Collaborating Faculty Member

GROUP MEMBERS

Post-Doctoral Researchers: Spyros Korkos (co-supervision)
PhD students: Oliver Santos-Lopes (co-supervision)
Research Scientist: Argyri Papagiannaki
MSc Research Assistants: Clio Kampitaki, Jessie Mertika, Kyriaki Louca (co-supervision)
Undergraduate thesis students: Maria Horkov, Nefeli Korka, Ioannis Mavromatis, Aristea Michalopoulou, Adelaida Pietri

BIOENGINEERING OF TISSUE CONSTRUCTS & MEDICAL DEVICES

Summary

We integrate cell biology, engineering, optics and in silico modeling to develop novel devices and systems based on Collagen-based Scaffolds (PCS). We study how cells and cell ensembles are regulated by their insoluble microenvironment (matrix) and engineer matrix analogs based on PCS. We design and fabricate complex tissue constructs based on PCS and evaluate their effects in cellular and animal models, emphasizing the Central Nervous System. Applications of interest include regenerative medicine, targeted delivery of therapeutics, 3D tissue models, brain-machine interfaces and medical robotics.

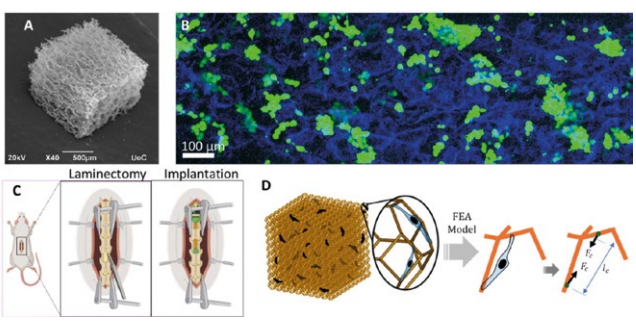
Current aims

- Characterize and optimize laser microfabrication of PCS.
- Develop methods for fabricating complex user-defined tissue constructs based on PCS.
- Develop treatments for CNS injuries (focus on Spinal Cord Injury) and neurodegeneration based on PCS-based delivery of Neural Stem Cells and/or small-molecule compounds. Evaluate their therapeutic effects in appropriate mice models.
- Develop human tissue models compatible with high-throughput quantification methods.
- Study the mechanobiology of cells inside microporous matrices. Focus on myofibroblast differentiation and its effect in wound healing and foreign body response.
- Develop and evaluate epidural spinal cord interfaces of enhanced temporal stability.

Progress in 2024-2025

The lab was established in January 2024. Since then, lab members have achieved the following

1. Set up lab premises at IMBB-FORTH. These include i) a biofabrication facility for scaffold fabrication (lyophilization) & cross-linking (DHT), PDMS casting, plasma treatment, and 3D printing, ii) a laser microfabrication facility for world-class fs laser ablation of biomaterials, polymers and tissues. Contributed to setting up a microfluidics facility (Charalampopoulos lab).
2. Progress within EIC Pathfinder project SoftReach: i) built prototypes of PCS implants that can be used for targeted therapeutic delivery via minimally-invasive robotic catheters (with U Thessaly & King's College London), ii) developed and characterized strategies for targeted delivery of small-molecule compounds via PCS (with U Cyprus, NHRF, and the Charalampopoulos Lab), iii) built an experimental fluidic setup for studying tissue-implant interactions.
3. Progress within FORTH Synergy project BioHySiC: designed epidural spinal cord electrode probes and developed appropriate probe implantation protocols in mice (with IESL-FORTH).
4. Quantified the 3D structure and rheology of microfibrillar collagen suspensions (with IESL-FORTH).
5. Developed efficient in silico models of microporous biomaterials (including PCS and certain types of 3D-printed scaffolds) mechanics, and used them to study the matrix stiffness perceived by cells grown inside microporous biomaterials (with U Cyprus).



A: SEM of a microfabricated PCS used to deliver NSCs in mouse SCI sites, B: Confocal imaging of human NSCs grown inside PCS, C: Schematic of procedures for the implantation of epidural spinal cord probes in mice, D: In silico modeling of the matrix stiffness perceived by cells inside microporous scaffolds.

Other activities

- Co-founded Reneurocell Therapeutics (2024), a spinoff company of FORTH and the University of Crete.
- Awarded a FORTH synergy grant on the development of long-term epidural spinal cord probes.
- Taught undergraduate (mechanics, thermodynamics, mechatronics) & graduate (biomaterials) courses, co-developed the "Makerspace/ Mechatronics/3D Printing lab" of the University of Crete.

Web page https://imbb.forth.gr/en/research/Dimitris-Tzeranis.40/

Publications

Georgelou K, et al. (2025) Delivery of Microneurotrophin BNN27 via Collagen Glycosaminoglycan Scaffold - FmocFF Hydrogel Grafts Promotes Neuroprotection after Optic Nerve Injury. **J Biomed. Mat. Res. B**: e70013

Achilleas Tsortos

Senior Staff Scientist

MOLECULAR BIOPHYSICS & BIOSENSORS

I am a Biophysicist, associate 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 R_g and intrinsic viscosity [η] of such linear macromolecules are described by scaling laws.
- Elucidating the physics of the acoustic sensor response (wave frequency and amplitude changes) when DNA chains are attached on the crystal surface in liquid environment. Besides its value as fundamental knowledge, this will help in the design of better sensing systems for use in nanobiotechnology.

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

Neuroscience

Ioannis Charalampopoulos

Professor / Medical School, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Post-doctoral researchers: Konstantina Chanoumidou, Maria Anna Papadopoulou
PhD students: Maria Kokkali, Despoina Charou, Alexandros Tsimpolis, Chrystalla Konstantinou
MSc students: Maria Peteinareli, Eleni Daskalaki, Despina Kritikaki
ERASMUS master students: Aman Kumar (University of Siena), Sina Bühler (University of Cologne)
Undergraduate thesis students: Kaliopi Tamvaki, Elisavet Valera, Anastasia Toska, Iro Efkarpidou, Angeliki Paraskevi Kyriakaki

NEUROPHARMACOLOGY / REGENERATIVE PHARMACOLOGY

Summary

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 analogues of their ligands with desired pharmacological properties, targeting adult neurogenesis and neuroprotection in mouse models of neurodegenerative diseases (Kokkali et al., 2025; Zota et al., 2025a, 2025b; Papadopoulou et al., under revisions), as well as in human induced Pluripotent Stem Cell-derived neural platforms, consisting of human neurons, microglia and astrocytes co-cultured in 3D scaffolds (Kourgiantaki et al., 2020; Charou et al., 2025; Chanoumidou et al., under revisions), in order to translate our basic research to pre-clinical therapeutic approaches.

Current aims

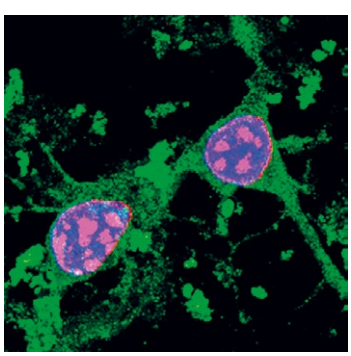
Targeting the endogenous regenerative capacity of nervous tissue, our strategic plan is to take benefit of our expertise on the development and pharmacological use of novel, patented neurotrophin analogs and use them as therapeutic agents for controlling hippocampal neurogenesis, neuronal survival against amyloid toxicity and enhancing cognitive performance in AD, while in parallel we develop humanized disease models that validate the mouse models. In order to transfer this basic knowledge to a translational opportunity, and in collaboration with pharmaceutical agencies, we will explore the efficacy of existing and new drugs against depression and diabetes, using human iPSC-derived neuronal and glial cells, while we aim to detect new biomarkers for neurodegenerative diseases. To ensure improved administration and more targeted drug or cell delivery to the brain, we will explore the use of soft nanorobotics for delivery of scaffold-based drug or cell delivery in neurodegenerative diseases, such as Alzheimer's Disease and Spinal Cord Injury, with specific products development from our spin-off, Reneurocell Therapeutic.

Progress in 2024-2025

During the last 2 years, our research team has managed to publish 8 research papers (4 original papers, 3 review papers and 1 editorial. Two recent research papers are under review. We have been granted with significant competitive grants from European Agencies (HORIZON2020, European Initiative Council) and national funds (Hellenic Foundation of Research and Innovation, Bodossakio Foundation), as well as collaboration with the pharmaceutical industry (Institute of Pharmaceutical Research and Technology, ELPEN Pharmaceutical company).
The Regenerative Pharmacology Laboratory had successfully granted to coordinate an EIC-PATHFINDER01, named SoftReach (www.softreach.eu) in order to develop soft nanorobotics system for less invasive drug administration in the brain.

Other activities

- Prof. Charalampopoulos served as the Director of the Graduate Program in Neurosciences and representative of the Medical School in the University Committee for Graduate Programs (2021-2024).
- Co-founder of the ReNeuroCell Therapeutics, spin off company of FORTH and UoC.
- Our lab is participating in the IMBB-Mentoring Program.
- Coordinator of the IMBB Translational Research Group and the Medical School Research and Innovation Committee.



Cover image for GLIA journal, Volume 72, Issue 4, 2024
(https://onlinelibrary.wiley.com/doi/abs/10.1002/glia.24399)
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.

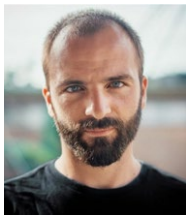
Web page http://regenera-pharm.med.uoc.gr

Publications

Kokkali M, et al. (2025) Multimodal beneficial effects of BNN27, a nerve growth factor synthetic mimetic, in the 5xFAD mouse model of Alzheimer's disease. **Mol Psychiatry** 30(6):2265-2283

Charou D, et al. (2024) Comprehensive characterization of the neurogenic and neuroprotective action of a novel TrkB agonist using mouse and human stem cell models of Alzheimer's disease. **Stem Cell Res Ther.** 15(1):200

Zota I, et al. (2024) Dynamics of myelin deficits in the 5xFAD mouse model for Alzheimer's disease and the protective role of BDNF. **Glia** 72(4):809-827



Emmanouil Froudarakis

Assistant Professor / Medical School, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Principal Staff Scientist: Athanasia Papoutsi
Postdoctoral researchers: Maria Diamantaki, Constantina Georgelou
PhD students: Stamatis Aliprantis, Christos Paschalidis, Ilianna Madouka
Research Assistants: Alexandros Evangelou, Zoe Dogani, Elissavet Anna Petsalaki
MSc students: Asimenia Goniotaki, Odysseas Raos, Anastasios Gratsaki
Undergraduate thesis student: Andreas Papadakis
Lab Manager: Agapi Ntretaki

SYSTEMS NEUROSCIENCE

Summary

Our lab uses object recognition in mice as an experimental framework to understand how cortical circuits extract, integrate, and utilize sensory information to guide perception and behavior. Natural scenes contain a multitude of objects that vary across time, space, and modality, yet the brain can effortlessly identify them under diverse conditions. Despite extensive progress in sensory neuroscience, the computational and circuit-level mechanisms that allow the cortex to form untangled, transformation-invariant object representations remain largely unknown. Understanding these mechanisms would represent a major advance in our knowledge of cortical computation and cognition.

To address these questions, we combine high-throughput behavioral training, large-scale neural recordings (two-photon, widefield, and Neuropixels electrophysiology), and computational modeling to study how population activity across multiple cortical regions evolves with experience and supports recognition and decision-making. Using closed-loop paradigms, we investigate the causal relationships between neural representations and perceptual outcomes.

Current aims

The group's research focuses on understanding:

1. How neural representations of objects evolve across the cortical hierarchy, and how inter-areal communication optimizes computation for specific behavioral demands.
2. How multisensory and contextual signals modulate sensory processing to support flexible and robust perception.
3. How local microcircuits interact with large-scale cortical networks to encode sensory information, make decisions, and adapt through learning.
4. How these mechanisms are altered in models of cortical dysfunction, such as neurodegenerative and neurodevelopmental disorders.

By leveraging object recognition as a tractable behavioral model, we study the transition from sensory encoding to cognition, linking neuronal dynamics with perception and action. This approach provides a unifying framework to investigate how distributed neural populations compute and coordinate behavior, offering insights into both normal and impaired cortical function. Ultimately, our research aims to build quantitative models that bridge neuronal activity, circuit architecture, and behavior, providing mechanistic understanding of cortical computation across scales.

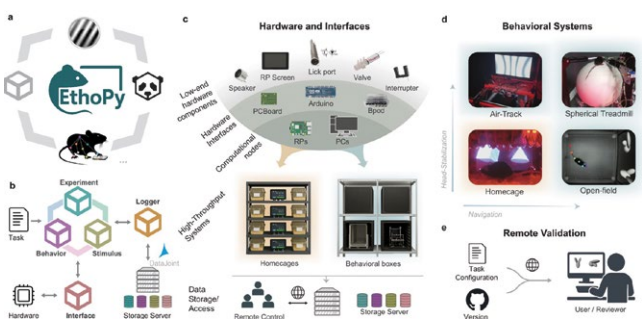
Progress in 2024-2025

During the current reporting period, we established a comprehensive experimental framework that integrates behavior, large-scale neural recordings, and computational modeling.

We developed and published EthoPy, a software platform that enables automated, high-throughput, and low-cost behavioral training directly in the animals' home cage. This system allows the efficient training of mice on complex perceptual and cognitive tasks with minimal experimenter intervention. In parallel, we established an open-field behavioral setup in which visual stimuli and task parameters are dynamically adapted based on real-time tracking of animal behavior. We are further developing a multisensory virtual environment that allows head-fixed animals to navigate using visual and non-visual cues.

Crucially, these behavioral platforms are now combined with newly established state-of-the-art neural recording infrastructure, including a Multiphoton Mesoscope for large field of view multiarea recordings and Neuropixels probes for large-scale chronic electrophysiological recordings. Importantly, during this period we have successfully established chronic Neuropixels recordings, enabling stable, long-term monitoring of hundreds to thousands of neurons across multiple cortical areas during learning and behavior. This capability represents a major technical milestone for the lab and enables longitudinal studies of circuit dynamics with unprecedented resolution.

Using these tools, we implement closed-loop experimental paradigms that integrate large-scale, multi-area neural recordings with deep learning–based modeling approaches. This framework allows us to construct a digital twin of the mouse visual cortex, enabling detailed characterization of stimulus selectivity, feature representations, and functional interactions across the visual hierarchy. Ongoing work focuses on understanding how neural invariances emerge across cortical areas and how they are shaped by low-level stimulus statistics and behavioral context, as well as how plasticity affects neural representations.



Other activities

- Dr. Froudarakis holds the position of Assistant Professor at the University of Crete Medical School and contributes to the graduate programs "Brain and Mind" and "Neurosciences".
- Dr. Froudarakis is a FENS–Kavli Scholar and currently serves as General Secretary of the Hellenic Society for Neuroscience (HSfN).
- In 2025, Dr. Froudarakis co-organized the FKNE Scientific Symposium 2025 in Heraklion, Crete.

Web page https://www.imbb.forth.gr/en/research/Emmanouil-Froudarakis.42/

Publications

MICrONS Consortium (2025) Functional connectomics spanning multiple areas of mouse visual cortex. **Nature** 640:435–447

Evangelou A, et al. (2025) EthoPy: Reproducible Behavioral Neuroscience Made Simple. 2025.09.08.673974 Preprint at https://doi.org/10.1101/2025.09.08.673974

Ding Z, et al. (2025) Functional connectomics reveals general wiring rule in mouse visual cortex. **Nature** 640:459–469

Domna Karagogeos

Professor Emeritus as of Oct 2024 / Medical School, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Senior Staff scientist: Kostas Theodorakis
Postdoctoral Researchers: Dimitrios Spyridakos, Niki Ktena
PhD students: Stefanos Kaplanis, Sofia Petsangouraki
MSc students: Iliana Agapi Goula, Ioannis Zyganitidis, Alexandra Tsakalidou
Undergraduate thesis students: Danae-Maria Polymili, Vassilios Ieremiadis, Emmanouli Karatheodorou, Enea Chasa, Sofia Karagianni, Emmanouela Zoumboulaki

NEURAL DEVELOPMENT AND MYELINATION

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 myelination/remyelination c) investigating the role of autophagy in myelin homeostasis in the central nervous system (CNS).

In parallel, we are analyzing the myelin content on hippocampal interneurons which provide the balance of excitation and inhibition and are implicated in neurodevelopmental pathologies.

Current aims

a) **CNS myelin homeostasis and disruption.** We focus on the role of autophagy in oligodendrocytes as an essential mechanism of myelin homeostasis. By ablating or inducing autophagy we are analyzing the myelin status using in vitro, ex vivo and in vivo models in adult and aged mice.

b) **Myelination properties of hippocampal interneurons.** Recently it was discovered that the majority of myelin in the hippocampus is found on axons of interneurons. We aim to understand the function of myelinated interneurons using a Cre-loxP system that will specifically ablate CNTN2/TAG-1 expressed by axons of neurons and oligodendrocytes (OL).

c) **The role of the cell adhesion molecule Contactin-2 in synapses.** CNTN2 is implicated in cell adhesion, neurite outgrowth, guidance, fasciculation, and the organization of subdomains of the nodes of Ranvier in myelinated axons. Results from animal models targeting CNTNs and their co-receptors CNTNAPs demonstrate their implication in neurodevelopmental pathologies and other diseases of the CNS. We will investigate the role of CNTN2 in synaptic compartments.

Progress in 2024-2025

a) We showed that the maintenance of myelin homeostasis in the CNS requires a functional autophagic machinery. Using *in vitro* and *in vivo* approaches, we demonstrated that oligodendroglial autophagy inactivation leads to significant alterations in myelin protein levels. Moreover, ultrastructural analysis revealed myelin deficits and increased degeneration of axons, accompanied by apoptosis. Behaviorally, aged knockout (cKO) mice exhibited deficits in learning and memory tasks, indicative of cognitive impairment. Additionally, we observed increased activation of microglia, suggesting an inflammatory response linked to the absence of autophagic activity in OLs. These results underscore the critical role of autophagy in oligodendrocytes for the preservation of CNS myelin and axonal integrity during aging. Our study highlights autophagy as a vital mechanism for neural maintenance, offering potential therapeutic avenues for combating age-related neurodegenerative diseases (Ktena et al, 2025). Furthermore, autophagic induction by utilizing caloric restriction mimetics enhanced both myelination and remyelination, through a direct effect in microglia promoting a less inflammatory environment (Kaplanis, Spyridakos et al, 2025 submitted).

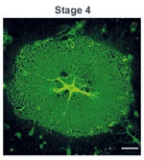
We employed a mouse model of excitotoxic brain injury, induced by the glutamate analogue, AMPA. We evaluated pathophysiological changes and investigated the potential neuroprotective properties and myelin status mediated through direct activation of the CB1 receptor after injury. Our data suggest that the endocannabinoid system, particularly the CB1 receptor, can reduce inflammation and promote remyelination—two critical therapeutic responses that could prove beneficial in the treatment of excitotoxicity (Spyridakos et al, in preparation).

b) **Hippocampal Interneuron myelination.** We showed myelination defects in somatostatin interneurons in Cntn2$^{-/-}$ mice. Myelin defects are accompanied by defects in the intrinsic properties of Sst+ interneurons (Petsangouraki et al, submitted).

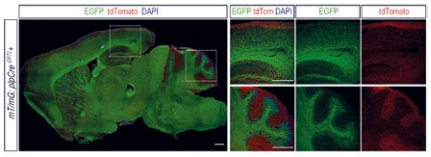
c) **The role of CNTN2 in synapses.** We have observed significant LTP reduction, spine density/maturation and behavioral changes in the Cntn2$^{-/-}$ mice. CNTN2 is present in both pre and postsynaptic compartments while proteomics indicate candidate pathways (in progress)

Collaborative studies

Together with the group of E. Stratakis (IESL) we are working on a new non-invasive method of myelin labeling using third harmonic generation microscopy in our ELIDEK project MAYA. In addition, we have characterized oligodendrocytes and myelin in collaborative work with the groups of I. Kazanis and G. Garinis as well as the properties of glial cells grown on novel scaffold materials (collaboration with M. Chatzinikolaidou, IESL).



A mature oligodendrocyte expressing MBP (in green) Scale bars: 30 μm.



Confocal images reveal green fluorescence in myelin tracts only in *plpCre+* transgenic mice. Rectangular boxes indicate the corpus callosum and cerebellum) magnified to the right.

Other activities

- D. Karagogeos has been awarded the first-class prize in the Physical sciences “E. Foteineli-I. Kritikou” in 2025 by the Academy of Athens for her work pertaining to myelin and Multiple Sclerosis.
- She has been elected to the IBRO (International Brain Research Organization) Pan-Europe Regional Committee (PERC) that focuses on supporting and promoting neuroscience.
- She is a member of the FENS (Fed. of European Neuroscience Soc) -Committee of Higher Education and Training which supports higher education and training in neuroscience.
- She was a member of the Recruitment and Training Working Group of EU Life and a member of the first IMBB Mentorship Committee.
- She is a member of the EC and vice-president of HELANA (Hellenic Academy of Neuroimmunology)
- She is teaching Biology to medical students and Neurobiology in 3 graduate programs.

Web page https://www.imbb.forth.gr/en/research/Domna-Karagogeos.44/

Publications

Ktena N, et al. (2025) Disruption of Oligodendroglial Autophagy Leads to Myelin Morphological Deficits, Neuronal Apoptosis, and Cognitive Decline in Aged Mice. **GLIA** 73(7):1383-1397

Dimitriou C, et al. (2025) Platelets regulate neural and oligodendroglial progenitors when infiltrating the brain parenchyma. **Commun Biol** 8(1):1640

Arvanitaki ES, et al, (2024) Microglia-derived extracellular vesicles trigger age-related neurodegeneration upon DNA damage. **Proc Natl Acad Sci USA** 121(17):e2317402121

Panayiota Poirazi

Research Director

GROUP MEMBERS

Postdoctoral researchers: Spyridon Chavlis, Eirini Troullinou, Michalis Pagkalos
PhD students: Ioanna Pandi, Maria Protopapa, Roman Makarov, Simone Tasciotti, Ioannis-Rafail Tzonevrakis, George Baxevanis
Graduated: Kostas Petousakis, Panagiotis Bozelos
MSc students: Erinni Mantouvalou, Georgia Sofokleous, Zeinab Ahmadi, Agapi Sarakini
Graduated: Nikos Falalakis, Anna Tsiamanta, Elisavet Karapanou, Chris Karageorgiou – Kaneen
Undergraduate thesis students: Chrysa Magaliou
Graduated: Chystalla Vasiliou, Michalis Ierodiakonou
Lab manager: Marsa Velissariou
Research assistant: Aleksi Sallo

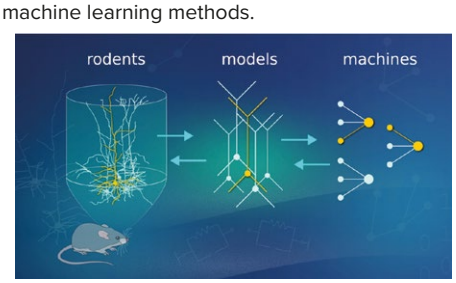
SYSTEMS NEUROSCIENCE

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. Our **mission** is to decipher the role of dendrites in complex brain function in health and disease and translate our findings into intelligent applications. We tackle this problem using a multidisciplinary approach that includes computational modeling of neurons and circuits, in vivo experiments in mice and neuro-inspired machine learning methods.

Current aims

We currently investigate how dendrites contribute to complex behaviors, using a combination of computational models and mouse experiments. We focus on learning and memory, navigation and behavioral flexibility. Leveraging our neuroscience findings, we integrate key dendritic features in machine learning algorithms, aiming to advance their efficiency and computing capabilities. Finally, we are building a platform that uses models to replicate disease states in cultured neurons and explore its potential to serve as a smart drug screening device. We are also exploring possibilities for commercializing our neuro-AI machine learning methods.



Progress in 2024-2025

Over the past two years, we have made substantial contributions to neuroscience and bio-inspired artificial intelligence.

Experimentally, we secured major funding, including an HFRI–SNF grant (€1.25M) linked to an ERC AdG evaluation. The experimental infrastructure was expanded to support dual imaging, and the team grew with the addition of new PhD, MSc, and undergraduate students. Our first experimental results on spine dynamics in flexible behavior were presented at multiple conferences (GRC Dendrites 2025, FENS Brain Conferences 2025 & 2024, Mediterranean Neuroscience Conference 2025). Our first experimental PhD and the respective publication are nearly complete, while a collaboration with an IMBB lab (N. Kretsovali) resulted in a joint manuscript.

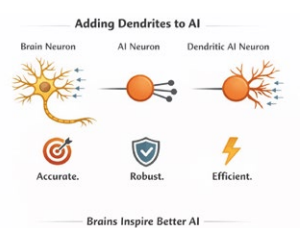
On the theoretical and computational front, we made several important discoveries: 1) incorporating dendritic structure and sampling properties into artificial neural networks leads to more accurate, robust, and parameter-efficient learning (*Nature Communications*, 2025); 2) with international collaborators, we showed that memories formed close in time are stored within the same dendritic segments through spine clustering (*Nature Neuroscience*, 2025), confirming earlier model predictions; 3) we contributed to a major study showing that different classes of inhibitory interneurons employ distinct dendritic integration strategies (*Neuron*, 2025); and 4) we demonstrated how synaptic spatial distribution shapes spatial tuning in CA1 neurons (Tasciotti, *bioRχiv*, 2025).

The lab has also shaped conceptual discourse through invited reviews and opinion articles advocating a dendro-centric view of brain computation and artificial intelligence (CONB 2023, 2024), leading to numerous invited talks at international conferences. The NEUREKA project we coordinate was highlighted as a success by the European Commission's CORDIS platform.

Together with technology experts, we demonstrated that dendritic models implemented on FPGA hardware yield significant energy, size, and runtime advantages (*TechRxiv*, 2025). We also released **DendroTweaks**, a tool for interactive exploration of neuronal models (*eLife*, 2024).

Other activities

- Dr. Poirazi received the 2024 FORTH Best Research Award (w. G. Garinis) and was an invited speaker in prestigious international meetings: Neuro-AI Workshop at NIH, US; CapoCaccia School on Neuromorphic Engineering, Italy. Plenary speaker at Bernstein Conference 2025, Germany; Dynamics Days Europe 2025, Greece; Neuromorphic Computing Nature conference, 2024 China; ICNCE 2024, Germany. In leadership roles, Dr. Poirazi was elected Chair of the Scientific Advisory Board of IMBB and appointed Secretary General of FENS (2024).
- Lab members also received multiple prestigious awards. I. Pandi: 2025 FENS/IBRO-PERC exchange fellowship, 2024 Michalis Karatzis PhD thesis award, invited talk at MSN2025; S. Chavlis: invited speaker at Bernstein Conference Workshop 2025, CNS Workshop 2025, FENS Regional Meeting Symposium 2025, Bernstein Conference Workshop 2024. E. Troullinou CNS 2025 Travel Award, S. Tasciotti and I. Pandi: GRC Dendrites 2025 Travel Awards.
- The lab contributed to organizing the first Brain Conference in Crete (2025) and actively engages in public outreach through European Researcher's Night.



Web page www.dendrites.gr

Publications

Chavlis S and Poirazi P (2025) Dendrites endow artificial neural networks with accurate, robust and parameter-efficient learning **Nature Communications** 16: 943

Sehgal M, et al. (2025) Compartmentalized dendritic plasticity in the mouse retrosplenial cortex links contextual memories formed close in time. **Nature Neuroscience** 28:602–615 (*co-corresponding author)

Makarov R, et al. (2025) DendroTweaks: An interactive approach for unraveling dendritic dynamics. **eLife** https://doi.org/10.7554/eLife.103324.3

Kyriaki Sidiropoulou

Associate Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Post-doctoral researcher: Angeliki Velli, Lida-Evmorfia Vagiaki
PhD students: Konstantinos Diskos
MSc students: Chrysoula Iordanidou, Zoe Drakaki
Undergraduate thesis students: Dimitris Antoniadis, Marina Paschalidou, Maria Nazou, Vasilis Kozanidis, Kyriaki Mastaka

NEUROPHYSIOLOGY & BEHAVIOR

Summary

Research in the "Neurophysiology and Behavior" laboratory focuses on the following topics: 1) to study the development of cellular mechanisms involved in the function of the prefrontal cortex, a brain area that matures very slowly across postnatal development 2) to investigate the developmental neurobiological alterations that occur in a mouse model of schizophrenia and 3) to study the therapeutic actions of novel anti-epileptic drugs.

Current aims

Our current aims include:

1. to delineate the developmental trajectories of neurophysiological mechanisms in the prefrontal cortex, in control mice and an animal model of schizophrenia
2. to investigate whether normalizing the observed adaptations at a specific developmental window can rescue the social and cognitive deficits as well as the neurophysiological adaptations in the schizophrenia animal model
3. to investigate the synaptic properties of prefrontal cortical neurons in a circuit-specific manner
4. to study the mechanism of action of novel anti-epileptic drugs.

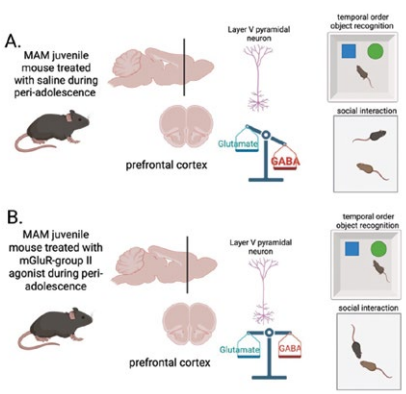
Progress in 2024-2025

1. We have identified differential neurophysiological adaptations in neonatal and adolescent MAM mice, an animal model of schizophrenia that has been validated in our lab (Chalkiadaki et al., 2019). Specifically, we identified increased spontaneous inhibitory currents in neonatal MAM mice, leading to reduced excitation-inhibition (E/I) ratio, compared to controls. On the other hand, adolescent MAM mice exhibited decreased spontaneous inhibitory currents leading to increased E/I ratio, compared to their respective controls.
2. Focusing further on the adolescent period, we treated peri-adolescent MAM mice with an agonist of the group II metabotropic glutamate receptors, which normalizes the increased E/I ratio, and we found that this treatment reversed the social and temporal memory deficits in MAM adolescent mice, as well as the increased excitation-inhibition ratio. These results were presented by Konstantinos Diskos, the Ph.D. student who leads this project, in the joint Hellenic Society for Neuroscience-European Society for Neurochemistry meeting in Naxos in May 2025.
3. We can tag prefrontal cortical neurons in a circuit specific manner using the retrograde tracer cholera toxin B. We studied prefrontal cortical neurons that project to the contralateral prefrontal cortex or to the amygdala. We find that the prefrontal cortical neurons that project to the amygdala received greater excitatory synaptic input compared to the prefrontal cortical neurons that project to the contralateral cortex.
4. We have identified that cannabidiol (CBD) and novel drugs that activate the GIRK channels (GIRK activators) act synergistically to reduce epileptic activity in hippocampal brain slices. A likely mechanism of action is the TRPA1 channel that could be a target for both CBD and GIRK activators. This project is in collaboration with Prof. Diomedes Logothetis of Northeastern University.

Other activities

- Dr. Sidiropoulou organized a symposium titled "Neuronal oscillations and brain network dynamics in health and disease" during the joint meeting of the Hellenic Society for Neuroscience and European Society for Neurochemistry, in Naxos in May 2025, while Konstantinos Diskos gave an oral presentation of his work at the same meeting.
- Lida-Evmorfia Vagiaki received a travel award to attend the FENS2024 meeting in Vienna.
- Dr. Sidiropoulou organized a workshop for miniscope imaging in freely-moving mice. Dr. Peyman Golshani, Dr. Daniel Aharoni and members of their labs visited FORTH for a hands-on workshop.

Pictures from the Miniscope workshop organized at FORTH, in July 2024



A. Mice that were exposed to MAM during gestation exhibit impaired prefrontal cortical function in adolescence, as indicated by increased excitation-inhibition ratio, as well as reduced temporal memory and reduced social interaction. B. MAM mice that were treated with an agonist of the metabotropic glutamate receptors during the peri-adolescence period restore their prefrontal cortical function to control levels. Specifically, the excitation-inhibition is normalized, the temporal memory function is improved and the social interaction with other mice is increased.

Web page www.sidiropouloulab.com/home

Publications

Vagiaki L-E, et al. (2025) Region-specific modulation and predictive potential of the oscillatory dynamics. **Neuroscience letters** 866:138367

Stavroulaki* V, Vagiaki* L-E et al. (2025) Effects of working memory training on cognitive flexibility, dendritic spine density and longterm potentiation in female mice, **Behav. Brain Res**. 115555

Spanaki* C, Sidiropoulou* K, et al. (2024) Glutamate-specific Gene Linked to Human Brain Evolution Enhances Synaptic Plasticity and Cognitive Processes. **iScience** 27(2):108821. eCollection 2024 Feb 16. *equal first author

Konstantinos Theodorakis

Senior Staff Scientist - Karagogeos Lab

NEURAL DEVELOPMENT

My main 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. During the period 2024 - 2025 I have been involved in the projects (P.I., Prof. D. Karagogeos):

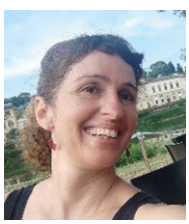
1. Mechanisms of regulation of myelination in Sst+ hippocampal interneurons (paper in preparation)
2. Resveratrol enhances remyelination following a demyelinating insult by promoting an anti-inflammatory environment(paper in preparation)

Since 2018 in collaboration with the Laboratory of Polymer Chemistry and Technology of AUTh I have participated in four research projects concerning the use of biobased materials and biocompatible nanomolecules for drug encapsulation, drug delivery, targeting and treatment. More specifically:

1. The main goal of the first project was the use of novel nanoparticles to deliver known agents that could improve remyelination in vivo. In particular, we employ innovative nanocarriers for the targeted and prolonged treatment of demyelinating diseases of the central nervous system.
2. 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 (paper in preparation)
3. Design and Evaluation of Biodegradable Zwitterionic PLA-Based Nanoparticles for pH-Responsive Tumor-Targeted Drug Delivery (published Sept 2025, https://www.mdpi.com/2073-4360/17/18/2495)
4. Synthesis and Evaluation of Biodegradable Folic Acid-Functionalized PLA-Based Nanoparticles for Targeted Delivery of Paclitaxel (paper submitted).

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 complex 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 can be dynamically regulated, how they are integrated at the circuit level, and how they are linked to specific processes or functions underlying behavior, such as flexible learning during decision making. We are also interested in how this machinery is dysregulated in pathological conditions. To achieve these goals, we combine computational models at different levels of abstraction, along with behavioral and physiological studies in vivo in mice, focusing mainly on the prefrontal cortex.

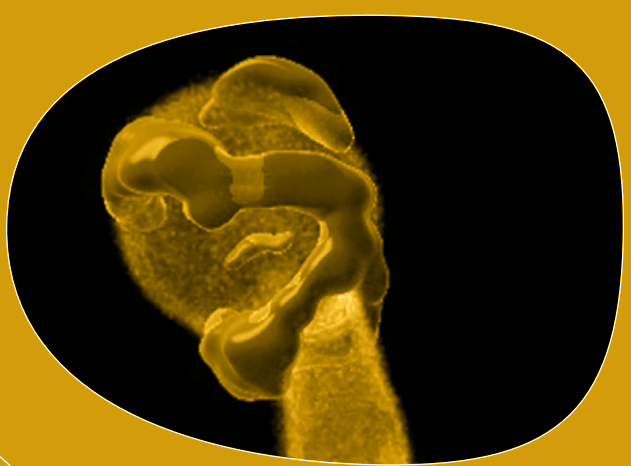
In 2024, I was elected an IBRO - PERC Committee affiliated member and to the Board of Directors of the Organization for Computational Neuroscience Society (OCNS), and I participated in the organization of the OCNS meeting in Natal, Brazil (2024) and the 16th Advanced Scientific Programming in Python Summer School in Heraklion, Greece (2024).

My publications in 2024-2025 are:

1. Evangelou, A., Diamantaki M., Georgelou K., Drakaki Z., Ntanavara L., Gerardos G., Morou S., Chatziris N., Dogani Z., Petsalaki E. A., Raos O. N., Gratsakis A., Papoutsi A., Froudarakis E. 2025. EthoPy: Reproducible Behavioral Neuroscience Made Simple. bioRxiv. doi: 10.1101/2025.09.08.673974.
2. Nordentoft M.S., Takahashi N., Heltberg M. S., Jensen M. H., Rasmussen R. N., Papoutsi A. 2024. Local changes in potassium ions regulate input integration in active dendrites. PLoS Biol. 22(12): e3002935. doi: 10.1371/journal.pbio.3002935. *Selected PLoS Biology Issue Image | Vol. 22(12) January 2025

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

Immunity



George Bertsias

Professor / Medical School, University of Crete
–Collaborating Faculty Member

GROUP MEMBERS

PhD students: Dimitra Nikoleri, Sofia Papanicolaou
MSc students: Evangelia Papagrigoraki (graduated), Arianna Cimmarrusti, Dimitrios Koupas, Maria Plakogiannaki

SYSTEMIC AUTOIMMUNITY, INFLAMMATION AND GENE REGULATION

Summary

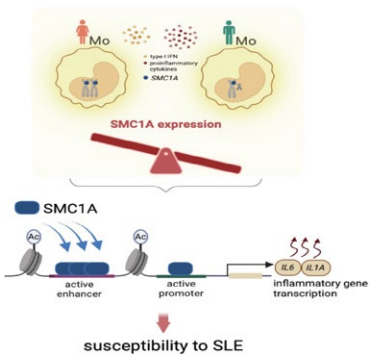
Our focus is on the regulation of innate and adaptive immunity, focusing on molecular, epigenetic and metabolic pathways implicated in autoimmunity. We use human and murine Systemic Lupus Erythematosus (SLE) as a disease-model, and apply targeted assays and high-throughput technologies in tissues in order to decipher the genomic basis of specific phenotypes (such as sex bias, disease activity/severity) and outcomes (response to targeted therapies, fibrosis/irreversible organ damage) of autoimmunity.

Current aims

- 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. Our results indicate that under the effect of IFN-alpha, BAFF is directed into autophagy vesicles and excreted via exosomes. BAFF-containing exosomes are increased in the blood stream of SLE patients compared to healthy individuals.
- 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. Using a combination of immunofluorescence and flow cytometry techniques, we found that lupus-affected kidneys have increased frequencies of myofibroblasts expressing aSMA and/or collagen. Ongoing experiments are focused on isolating these cells, to undergo gene profiling and functional studies ex vivo and in vivo.
- In collaboration with the group of P. Verginis, we are exploring the **molecular basis underlying dysfunction regulatory CD4+ T-cells (Trgs) in SLE**. Our approach involved single-cell RNA-sequencing of FACS-sorted Tregs, coupled with proteomic analysis and ATAC-seq, to proble the epigenetic landscape of these cells. Preliminary result show that Tregs from active disease show upregulation of interferon- and inflammation-related pathways, potentially linked to enhanced glycolysis.

Progress in 2024-2025

- Driven by our results from a blood RNA-sequencing study in a large cohort of individuals with lupus, we characterized the role of the chromatin architectural factor SMC1A/cohesin in regulating immune responses in female versus male monocytes. Notably, SMC1A is a female-biased factor which, during lupus autoimmunity, gains access to inflammatory enhancers and stimulates the transcription of immune genes, thus conferring susceptibility to immune-mediated disorders (Figure).
- In another study, we explored how interferon-alpha, a hallmark cytokine implicated in autoimmunity, can modulate intracellular metabolic pathways involved in monocyte activation. By the use of biochemical, immunochemical, transcriptome and high-throughput technologies, we found that chronic exposure of monocytes to interferon induces a transcriptional program of cholesterol biosynthesis, resulting in intracellular accumulation of cholesterol and lipid droplets. Blockade of cholesterol de novo synthesis by the use of specific inhibitors reduces the inflammatory phenotype of monocytes, therefore suggesting that metabolic modulation can help to ameliorate inflammatory/autoimmune pathologies. A manuscript has been submitted for peer-review.
- 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 sex, thus proposing a role for this often-overlooked layer of transcriptome/molecular variation in autoimmunity.



SMC1A, a cohesin subunit that escapes X-chromosome inactivation, shows higher expression in female monocytes from SLE patients and under lupus-like conditions. In these conditions, SMC1A relocates to active immune gene regulatory regions, enhancing transcription. Its stronger binding to enhancers of inflammatory genes like IL6 and IL1A in females may drive their elevated expression. Consequently, SMC1A-regulated genes are upregulated in female SLE monocytes, aligning with their more inflammatory transcriptional and cytokine profiles compared to males. (obtained from Nat Commun. 2025; 16: 10350).

Other activities

- We continue our work on preclinical/early autoimmunity, through the establishment and maintenance of an at-risk cohort. Detailed clinical, immunological characteristics are monitored longitudinally, together with collection of biological specimens.
- In collaboration with the BRFAA and the Attikon Hospital (Rheumatology Unit), we performed transcriptome analysis (RNA-sequencing) in sequential blood specimens from SLE patients who received various therapies, in order to characterize the molecular basis accounting for insufficient treatment response.
- 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 and lupus nephritis.

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

Publications

Kosmara D, et al. (2025) The sex-biased chromatin modifier SMC1A promotes autoimmunity by shaping inflammatory pathways in patients with SLE. **Nat Commun.** 16(1): 10350

Garantziotis P, et al. (2025) Transcriptome analysis to decipher the molecular underpinnings of response to treatment in systemic lupus erythematosus. **RMD Open.** 11(1): e005050

Moysidou GS, et al. (2025) Molecular basis for the disease-modifying effects of belimumab in systemic lupus erythematosus and molecular predictors of early response: blood transcriptome analysis implicates the innate immunity and DNA damage response pathways. **Ann Rheum Dis.** 84(2): 262-273

Georgios Chamilos

Professor / Medical School, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers: Irene Kyrmizi, Tonia Akoumianaki, Ioannis Morianos, Zoi Veneti (left 2025), Akrivi-Dimitra Daskalaki
PhD students: Electra Nenedaki, Vasilis Nidris, Stavroula Baiba, Alexandra Vatikioti, Marina Gkountzinopoulou, Manthos Sertedakis
MSc student: Nikoleta Tavernaraki
Research assistant: Evangelia Eleni Kapetanaki

FUNGAL IMMUNOLOGY

Summary

Airborne filamentous fungi (molds) are increasingly important pathogens in an-ever expanding group of patients with complex immunometabolic defects. Over the last decade, the surge in development of precision-medicine therapies for malignant and autoimmune diseases, and the emergence of viral sepsis syndromes (e.g., influenza, COVID-19), has resulted in an unprecedented increase in incidence of invasive mold infections (IMIs) worldwide. IMIs are associated with limited response to antifungal therapy, substantial mortality rates (> 50%), and enormous economic burden. Understanding pathogenesis of IMIs remains a critical, unmet need for the development of novel, host-directed therapies and improve disease outcomes.

Current aims

Our group focuses on:

- Specialized immunometabolic programs in alveolar macrophages (AMs) regulating phagosome biogenesis and immune homeostasis in response to fungal infections
- Molecular mechanisms of neutrophil decision-making during interactions with fungi
- Novel metabolic antifungal host effectors
- Pathogenetic strategies employed by fungi to evade physiological immune responses
- Molecular mechanisms of immunodeficiency leading to development of IMIs

Progress in 2024-2025. Completed Projects:

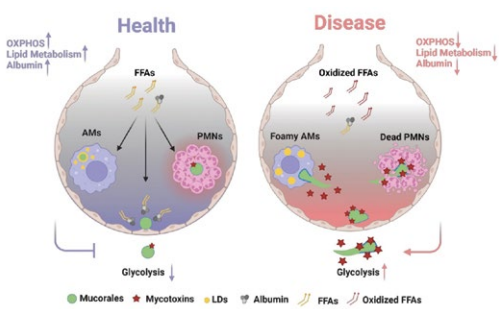
Our group uncovered a novel role of albumin in antifungal host defense. The study, now published in *Nature*, provides critical new insights into mucormycosis, a rapidly progressive and often fatal infection caused by Mucorales fungi. In this collaborative work, we found that patients with mucormycosis have significantly lower albumin levels than those with other fungal diseases. Importantly, hypoalbuminemia emerged as an the most significant predictor of poor clinical outcomes of patients with mucormycosis across multiple continents. The study further demonstrated that albumin potently and selectively inhibits the growth of Mucorales fungi, and that albumin-deficient mice are specifically susceptible to mucormycosis.

Mechanistic investigations revealed that albumin's antifungal activity is mediated by the free fatty acids (FFAs) bound to the protein. Albumin-bound FFAs inhibit protein synthesis in Mucorales, suppressing the production of key virulence factors and rendering the fungus avirulent in animal models. Importantly, albumin protects FFAs from oxidation, a process that abolishes their antifungal activity. Consistent with this mechanism, sera from mucormycosis patients exhibited increased FFA oxidation, providing a mechanistic explanation for their heightened susceptibility to infection.

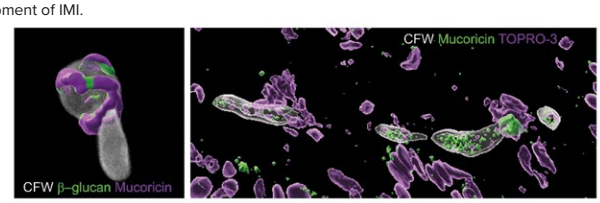
In parallel work (V. Nidris et al., Best Poster Award, *20th International Conference on Innate Immunity*, May 2025, submitted manuscript), we identified lipid-mediated antifungal defense program operating within alveolar macrophages (AMs). This study addresses a long-standing gap stemming from our earlier observations that fungal melanin inhibits Ca^{2+}/calmodulin signaling and arrests phagosome maturation (Kyrmizi I, *Nat Microbiol* 2018; Akoumianaki T *Cell Host Microbe* 2018& 2021, Andrianaki A, *Nat Commun*2018), while the downstream host effector mechanisms that restrict fungal growth within AMs remained unknown. Finally, we identified that coordinated neutrophil clustering (swarming) is a specialized host defense mechanism against Mucorales (S. Baimba et al., bioRxiv; under review in *Cell Host & Microbe*). Impaired neutrophil clustering in mucormycosis-predisposing conditions, permits mucoricin release, which in turn binds selectively to β-glucan on germinating Mucorales spores. This mucoricin-β-glucan complex formation creates a molecular trap that induces apoptosis of recruited neutrophils, disrupts swarming, and promotes invasive fungal disease. These findings define neutrophil swarming as a critical host defense program and a primary target of mucoricin-mediated immune evasion.

Other activities

- Hosted undergraduate and rotation students for training
- Coordinated a Multicenter National Study (Pro-sCAP) to dissect pathogenesis and complications of severe community acquired pneumonia
- Invited Lectures 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



Model on immunopathogenesis of mucormycosis. In healthy subjects, FFAs released from albumin suppress growth of and mycotoxin expression by inhaled spores. The uptake of spores by AMs triggers OXPHOS-mediated FFA inhibition of fungal growth. Neutrophil swarming eliminates germinating spores that escape from AM control. In subjects with metabolic abnormalities low albumin and elevated levels of oxidized FFAs promote the development of IMI.



Mucoricin disrupts neutrophil swarming. Left panel: Confocal microscopy demonstrating selective mucoricin binding to β-glucan–rich sites on germinating Mucorales. Right panel: Representative confocal image of a tissue biopsy from a patient with mucormycosis showing mucoricin-mediated disruption of neutrophil clusters.

Web page https://cmmp.med.uoc.gr/

Publications

Baimpa S, et al. (2025) Mucoricin binding to β-glucan sites on germinating Mucorales spores disrupts neutrophil swarming to promote pathogenicity. bioRxiv [Preprint]. doi: 10.1101/2025.10.28.685056. PMID: 41279284; PMCID: PMC12636483. (Under Review in **Cell Host & Microbe**)

van de Veerdonk FL, et al. (2025) Aspergillus fumigatus biology, immunopathogenicity and drug resistance. **Nat Rev Microbiol** 23(10):652-666.

Prodromos Sidiropoulos

Professor / Medical School, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers: Eirini Sevdali (PhD), Panagiota Goutakoli, Eirini Flouri (MD, PhD)
PhD students: Elpida Neofotistou Themeli
MSc student: Grigorios Zakkas
Research assistant: Maria Theoni Michalopoulou

REUMATOLOGY, AUTOIMMUNITY & INFLAMMATION

Summary

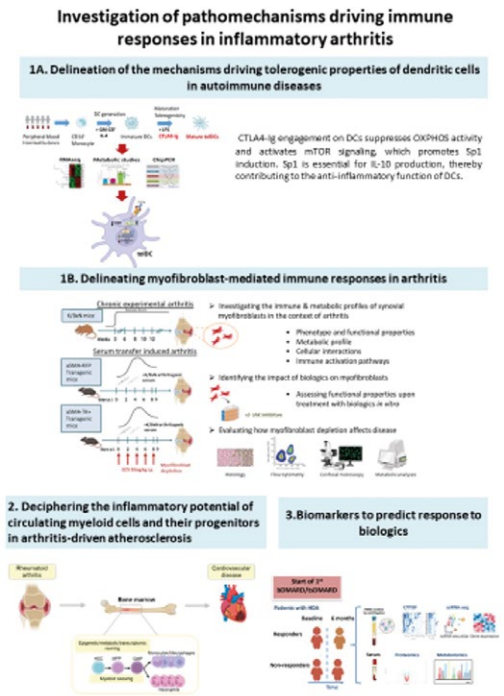
The Laboratory of Rheumatology, Autoimmunity and Inflammation of the Medical School together with the Rheumatology & Clinical Immunology Clinic at the University Hospital of Heraklion, represent an interdisciplinary group of physician scientists, bio-scientists, clinicians and nurses, which investigate 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 to investigate innate and adaptive immune responses. 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. Finally, 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 apply CTLA4-Ig as a tool to generate tolDCs and we study the molecular mechanisms contributing to tolDCs development.
   b) Fibroblasts are important contributors to the articular inflammation in RA. We currently explore their 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. **Driving mechanisms of atherosclerosis in the context of chronic inflammatory rheumatic diseases.**
   We apply mouse models of experimental arthritis (chronic and transient) in combination with an inducible model of atherosclerosis, as well as we study peripheral blood immune cells of RA patients with distinct inflammatory burden. We assess the hypothesis that chronic inflammation imprints a pro-inflammatory signature in progenitor myeloid cells generating circulating monocytes with increased atherogenic potential.
3. **Biomarkers to predict response to biologics in inflammatory arthritis.**
   In prospective studies we organize biobanks linked to well-characterized clinical dataset of patients starting biologic therapies (TNFα or IL-17 inhibitors) or JAK-inhibitors. We combine peripheral blood immunophenotyping, proteomics, transcriptomics and metabolomics in order to identify a "fingerprint" to predict individually clinical responses, in an effort to support personalized treatment.
4. **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 aim to define a molecular "fingerprint" to predict disease's outcome. In this context, we utilize high-throughput technologies (RNA-seq, methylomics, glycomics) in peripheral blood cells of patients.

Progress in 2024-2025

1. Finalized transcriptomic and methylomic analysis of whole blood in patients with early RA patients.
2. Defined a novel tolerogenic effect of CTLA4-Ig on dendritic cells.
3. We have established and we are expanding well characterized patients cohorts (RA, spondyloarthritis) in the local registry (UCRCR), combined to a biobank of serum, peripheral blood immune cells, DNA and RNA.
4. We have established three mouse models of experimental arthritis and one mouse model of arthritis/atherosclerosis.
5. We have shown that treatments of RA differentially regulate the lipid profile of those patients. Additionally, we have found that improvement of HDL properties in a mouse model of arthritis reduces arthritis severity by altering key cell subsets that drive disease pathogenesis.



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

Publications

Aymon R, et al. (2025) Incidence of Major Adverse Cardiovascular Events in Patients With Rheumatoid Arthritis Treated With JAK Inhibitors Compared With Biologic Disease-Modifying Antirheumatic Drugs: Data From an International Collaboration of Registries. **Arthritis Rheumatol.** 77(9):1194-1204

Dedemadi AG, et al. (2025) Dantrolene is an HDL-associated paraoxonase-1 activator with immunosuppressive and atheroprotective properties. **Biochim Biophys Acta Mol Cell Biol Lipids** 1870(2):159596

Bertsias A, et al. (2024) Patterns of comorbidities differentially affect long-term functional evolution and disease activity in patients with 'difficult to treat' rheumatoid arthritis. **RMD Open** 10(1):e003808.

Christos Tsatsanis

Professor / Medical School, University of Crete –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: Georgios Zormpas
Undergraduate thesis students: Sofia Makri, Asimina Ploumistou

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. Fibroblasts also participate in the initiation and propagation of inflammation and tissue homeostasis. Our work focuses on understanding the mechanisms regulating innate immune responsiveness and how changes induced by the micro- and macro-environments (diabetes, ageing, microbiome, inflammation) 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 2024-2025

In collaboration with Assistant Professor E. Vergadi, former postdoctoral fellow of the group, we published her work as Postdoctoral Fellow demonstrating 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).

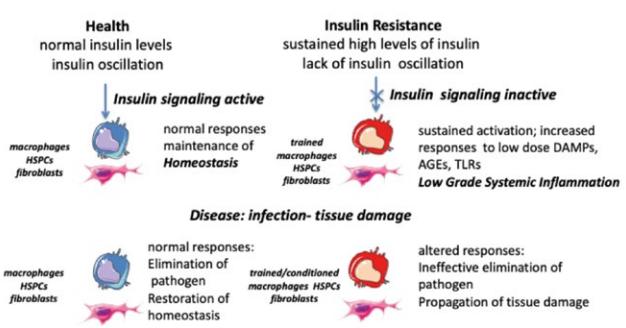
Our group also investigated the potential of fibroblasts to obtain a 'trained' phenotype in the context of inflammation and insulin resistance, just as we have previously shown for macrophages. We utilized the model of ligamentum flavum fibroblasts from patients. Akt2-/- mice and diet-induced diabetic mice and showed that fibroblasts obtain a distinct phenotype that propagates inflammation and hypertrophy. We demonstrated the underlying mechanisms that includes changes in the balance between Akt1 and Akt2 activation and in cell metabolism (J Immunol. 2025).

Work initiated in previous periods studying the impact of red algae-derived terpenes in adipocyte differentiation and obesity has been concluded. We showed that a brominated diterpene from Laurencia sp. possessed potent action in suppressing adipocyte differentiation in culture and, when administered in mice it prohibits weight gain. The mechanism includes suppression of glycolysis and lipid accumulation in adipocytes. The findings have been included in a patent application published PCT/WO2025/104209 22.05.2025.

Collaborative work funded by previous grants on the impact of the gut microbiome and particular probiotics on diabetes and hypercholesterolemia demonstrated that a novel probiotic strain reduces glucose intolerance and serum cholesterol by targeting cholesterol metabolic pathways (Microorganisms, 2024).

Other activities

- International fellows visited the lab for one month training under the EFLM exchange training program-EFLM-LabX (from Turkey, Finland, Italy, Latvia, Poland). Fellows from collaborating commercial partners from Serbia and Italy were seconded under the MSCA-SE program CardioSCOPE for training.
- We presented our work in national and international scientific conferences including the biannual congress of the European Federation of Laboratory Medicine (Euromedlab2025).



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

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

Publications

Vergadi E, et al. (2024) An IL-10/DEL-1 axis supports granulopoiesis and survival from sepsis in early life. **Nat. Commun**. 15(1):680

Paflioti E, et al. (2025) Diabetes and insulin resistance alters ligamentum flavum-derived fibroblast responses in an AKT2-dependent manner. **J Immunol.** 214(12):3543-3553

Daskalaki MG, et al. (2025) Epigenetic and metabolic regulation of macrophage responsiveness and memory. **J Immunol.** 214(11):2812-2821

Panayotis Verginis

Associate Professor / Medical School, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers: Aikaterini Hatzioannou
PhD students: Iosif Papafragkos, Miranta Papadopoulou, Athina Boumpas, Antonis Papaioannou, Efrossyni Markaki, Zacharias Papadovasilakis
Research assistant: Lydia Xenou

IMMUNE REGULATION

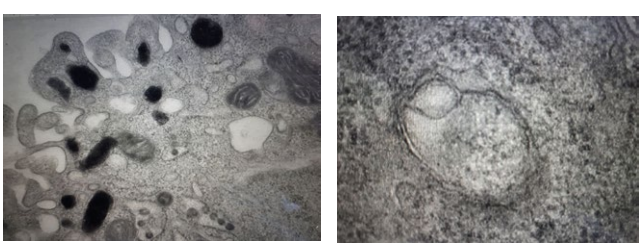
Summary

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 2024-2025

The main scientific directions of my lab are the following:

- **Investigating the role of tissue-reident Treg cells in cancer metastasis.**
  Rationale: Each tissue in the human body contains its own immune ecosystem. Recent evidence supports that Treg cells (similar to most cell of the immune system) possess unique properties depending on the tissue of residence. Therefore, in this aim, using mouse models of brain and bone marrow metastasis, we aim to shed light on how tissue-resident Treg cells influence metastasis and whether their presence impact on the effectiveness of cancer immunotherapy.
- **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.
- **Circulating Cancer associated fibroblasts (CAFs) direct cancer cell metastasis.**
  We recently demonstrated that CAFs form synapsis with Tregs in the tumor microenvironment, facilitating tumor growth (Varveri et al Nat Com 2024). This research direction aims to investigate the role of CAFs in tumor metastasis. Using mouse model that allow specific ablation of CAFs, combined with mouse metastatic models, we investigate how depletion of CAFs, at different time points during cancer cell dissemination, imprint on development on metastasis and the respective anti-metastatic immune response.
- **Identify mechanisms of resistance of immunotherapy with immune checkpoint inhibitors in patients with solid tumors.**
  Recently we published an extensive immune and transcriptomic profile derived from blood of patients with non-small cell lung cancer (NSCLC) responding or not to immune checkpoint inhibitor immunotherapy (Semitekolou et al iScience 2025). Currently, we focus on the understanding of the immune-mediated mechanisms that influence the response to immunotherapy with immune checkpoint inhibitors in patients with lung cancer, melanoma as well as head and neck cancer. Furthermore, a significant proportion of patients treated with immune checkpoint inhibitors, develop immune-related adverse events (resembling autoimmune reactions). Thus, through the extensive immune profiling, we aim to shed light in unrecognized mechanisms that underlie the development of the immune-related adverse events, to potentially facilitate the design of rationale immunotherapy with minimal adverse events and toxicities.



Autophagy in cancer associated fiborblasts in tumor microenvironemnt

Other activities

- Organization of “Immunology school for clinicians” (https://clinicalimmunology-crete-2025.gr)
- ELIDEK grant “**Deciphering the Role of Cancer Associated Fibroblasts in Immunotherapy Resistance and Tumor Metastasis**”

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

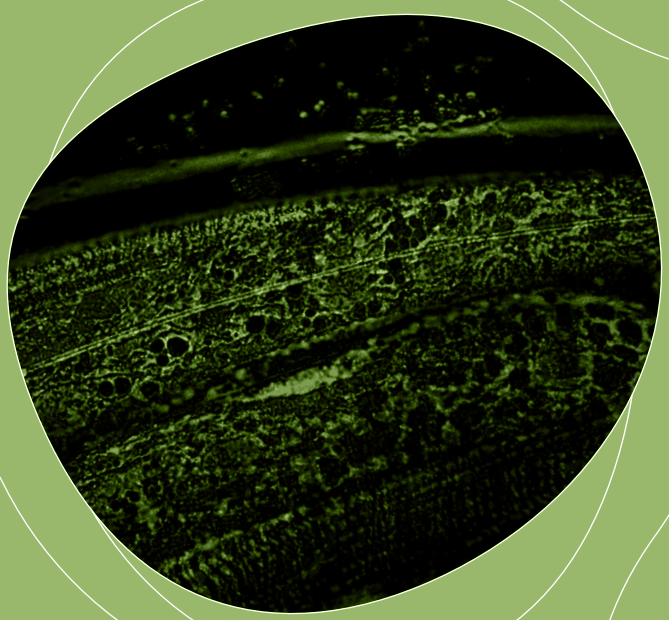
Publications

Semitekolou M, et al. (2025) Blood immunomap for prediction of responses to anti-PD-1 immunotherapy in metastatic non-small cell lung cancer. **iScience** 28(9):112804. eCollection 2025 Sep 19

Varveri A, et al. (2024) An Immunological Synapse Formation Between T Regulatory Cells and Cancer-Associated Fibroblasts Promotes Tumor Development **Nat Commun** 15(1):4988

Boumpas A, et al. (2024) PD-L1 blockade immunotherapy rewires cancer emergency myelopoiesis **Front Immunol.** 15:1386838. eCollection 2024

Evolution, Development & Cell Biology



Daphne Bazopoulou

Assistant Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

PhD students: Niki Astropekaki, Kyriakos Mavridis, Agapi Kavvadia, Christina Karagianni
MSc students: Aikaterini Kyriakaki (completed in 2025), Sofia Spinthaki (completed in 2024)
Undergraduate thesis students: Kyriaki Chouli (completed in 2025), Orestis Kontogiannis (completed in 2025), Maria Ntouni (completed in 2024)
Visitor-trainee: Veronika Mazrimaite

STRESS & AGING

Summary

Our lab explores the impact of early-life stressors on healthspan and longevity, integrating approaches from molecular biology, physiology, and bioengineering. Utilizing the model organism *Caenorhabditis elegans*, we are particularly interested in the role of reactive oxygen species (ROS) as signaling entities in
a) the regulation of aging and age-associated pathologies, and
b) host–microbe interactions.
Our research aims to elucidate ROS-dependent regulatory mechanisms and their spatiotemporal dynamics, with the overarching objective of informing the development of targeted interventions that enhance health and extend lifespan.

Current aims

Our previous studies have shown that variations in the endogenous ROS levels represent one of the long-sought after, early-life stochastic factors that individualize healthspan and lifespan. We now seek to understand how this transient presence of ROS exerts its long-term effects. Specifically, we investigate the extent to which changes in the redox-sensitive epigenome during development affect physiology later in life, aging and age-related pathologies.
ROS production has shown to increase healthspan and lifespan via adaptive responses that involve improved defense mechanisms and stress resistance. However, whether known longevity modulators act independently of ROS to regulate organismal lifespan, is yet unclear. To address this, we study

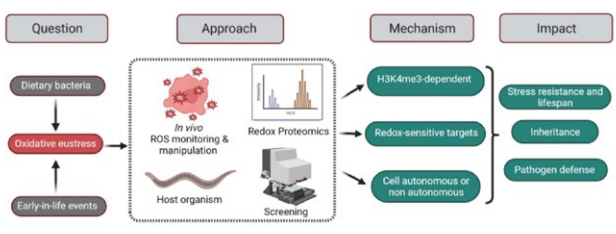
1. the role of ROS as a universally relevant signal for lifespan determination and
2. the implication of redox-regulated events as a downstream effector of longevity interventions.

We test the hypothesis that the early-in-life presence of certain microbiota in the *C. elegans* gut trigger the right amount of ROS production to activate redox-regulated pathways and increase host fitness and lifespan. Our goal here is to identify such pathways and explore temporal and spatial dynamics of ROS at the host-microbe interface in health and disease.

Progress in 2024-2025

Ongoing projects

- Developmental oxidative stress enhances later-in-life immune defenses and fitness of the *C. elegans* host
- A BTB domain-containing protein implicated in heat and oxidative stress tolerance in *C. elegans*
- The host-microbe redox interplay and its role in aging and neurodegeneration
- Caloric restriction and its interplay with redox signaling in lifespan and healthspan
- A microfluidic-based platform for investigating host-pathogen interactions
- Development of a Tunable and Reversible Linear Thermal Gradient Plate based on open-source modules for *C. elegans* thermotaxis assays



To mechanistically investigate the effects of ROS in *C. elegans* physiology, we employ a) in vivo imaging and optogenetic probes, b) redox proteomics and c) forward genetics.

Other activities

- Hosted the "1st Training Course in the Biology of Aging" (13-17 October 2025)
- Contributed to University of Crete Career Day 2025 with a Parallel Session "Career in Life Sciences Expectations, Planning & Pivoting"

Web page https://bazopouloulab.com/

Publications
Karagianni C and Bazopoulou D (2024) Redox regulation in lifespan determination. **Journal of Biological Chemistry** 300(3):105761

Ioanna Keklikoglou

Assistant Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers: Eirini Maria Giatagana, Amalia Vogiatzoglou
PhD student: Stergios Chatzisevastos
MSc students: Panayiotis Vouvopoulos, Nikoleta Tsiantouli, Anastasia Maroufidou, Theodora Tatsiou, Dimitrios Efthymiou

CANCER METASTASIS & IMMUNITY

Summary

Our group focuses on understanding the molecular and cellular mechanisms that mediate resistance to chemotherapy, mainly in breast cancer. Using state-of-the art mouse models of cancer, as well as quantitative molecular and cellular approaches, we are interested in dissecting the microenvironmental cues that orchestrate specific tumour responses and metastasis formation after chemotherapy. More specifically, we are interested in understanding how inflammation - and tumour-associated myeloid cells in particular - is linked to chemoresistance, to develop new therapeutic approaches for the treatment of metastatic breast cancer.

Current aims

Current projects in the lab include:

- Investigating the role of extracellular matrix in myeloid cell recruitment and chemoresistance
- Dissecting the functional role of cytoskeletal remodeling in the secretion of pro-tumoural extracellular vesicles, and cell plasticity during metastasis
- Understanding how chemotherapy and chemotherapy-elicited extracellular vesicles modulate the heterogeneity and function of myeloid cells in pre-metastatic and metastatic niches
- Dissecting the crosstalk of Alzheimer's disease with cancer development

Progress in 2024-2025

In the past two years, newly established lab has made important progress. Several students, at all levels, have performed their training under our guidance. Importantly, two of our 3 MSc graduates were offered a PhD position in prestigious institutions abroad.

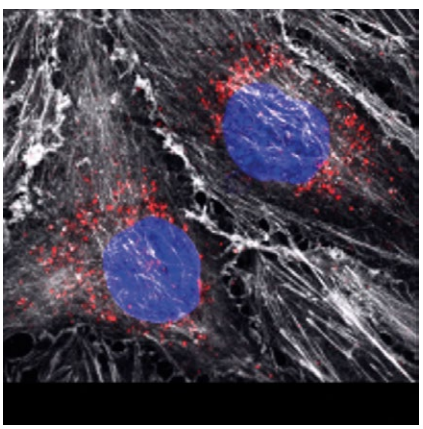
Moreover, our team has made significant contributions to the field of breast cancer chemoresistance:

i) We found that cancer cells rewire their transcriptional programs under the pressure of chemotherapy leading to a newly acquired phenotype, which renders them resistant to the treatment and metastatic (Moughari, Teigen et al, in revision).

ii) We found that fibroblasts alter the secretion of extracellular matrix deposition in response to chemotherapy thus altering the phagocytic capacity of tumour-associated macrophages. This work has been presented to the AACR meeting 2025 (oral presentation) and to the Crick International Cancer Conference 2024 (oral presentation) and won the best oral presentation award.

iii) We initiated the collection of matched patient samples (tissue and blood) from triple-negative breast cancer patients before and after neoadjuvant chemotherapy to verify our discoveries in humans. For this purpose, we have established a collaboration with the Translational Oncology Department of the Medical School of the University of Crete (Prof D. Mavroudis and Prof S. Angelaki).

Furthermore, our scientific interests have expanded into the emerging field of cancer-neuroscience crosstalk. Using transgenic mouse models as well as human samples from patients with Alzheimer's disease, that we have collected in collaboration with the Neurology Clinic and Prof I. Zaganas, we are investigating the heterotypic diseased brain-tumour interaction to better understand the mechanisms that modulate the reverse correlation in the incidence of these diseases.



Transfer of CD9-mCh+ cancer cell-derived extracellular vesicles to endothelial cells was assessed by immunofluorescence (confocal microscopy).

Other activities

- Dr Keklikoglou currently serves in the organization committee of the European Network for breast development and cancer (ENBDC)
- Dr Keklikoglou was an invited speaker to many national and international conferences such as the annual conference of Hellenic Society of Molecular Biology and Biochemistry (HSBMB) and the prestigious EMBO Symposium on "Defining and defeating metastasis".
- In 2026, the first FEBS Advanced Course on Tumour Microenvironment: From Tumour Heterogeneity to Therapy Resistance will take place in Fodele, Crete, organized by Dr Keklikoglou (main organizer) and Dr Verginis (co-organizer).
- Dr Keklikoglou received an EMBO Installation Grant (2025), a FEBS Excellence Award (2024), the Beug Foundation Metastasis Prize (2023) and the L'Oreal-UNESCO Women in Science Award (2023).
- Our lab also received competitive funding from Hellenic Foundation for Research and Innovation (Basic support for all sciences, Greece 2.0), and Fondation Sante.

Web page https://imbb.forth.gr/en/research/Ioanna-Keklikoglou.403/

Publications

Kyriakidis I, et al. (2024). DICER1 rs3742330 and AGO1 rs636832 polymorphisms and acute lymphoblastic leukemia in Greek children and adolescents: A case-control study. **Gene Reports** 37: 102043

Christos Delidakis

Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Senior postdoctoral researchers: Vasiliki Theodorou, Evanthia Zacharioudaki, Zoe Veneti
PhD students: Konstantina Kalodimou, Konstantina Kalodimou, Virginia Fasoulaki, Vassiliki Kapoulea
MSc students: Panagiotis Tsotoulidis, Georgia Karagianni, Orestis Kokolakis
Research assistant: Margarita Stapountzi
Undergraduate thesis students: Despoina Kritikaki, Christina Louka, Georgia Kourti, Selina-Agapi Andrianou, Vasilis Markos, Katerina Avetisian, Thanasis Fragkopoulos

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 decide what type of progeny cells to produce and when to do it. A central theme in our research is how the same signalling pathways and gene regulatory modules can be redeployed in different developmental and disease settings that involve neural or intestinal stem cells. A highly conserved signalling pathway in the entire animal kingdom, the Notch signalling pathway, and the E(spl)/Hes transcription factors are the molecules from which our various lines of investigation radiate. Our group has an extensive set of genetic tools to manipulate the CNS and gut cells and large expertise in immunohistochemistry, confocal microscopy and genomics.

Current aims

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. 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)
4. We investigate how Notch regulates the expression of the Hey TF during asymmetric cell divisions in the CNS and intestine. (with Maria Monastirioti)

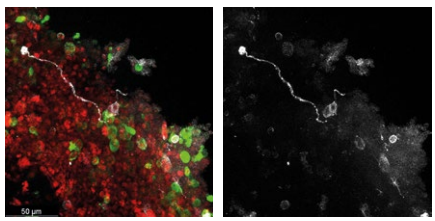
Progress in 2024-2025

Embryo project:

We had shown earlier that achaete-scute (ASC) TFs are not needed for neuroblast delamination from the ectoderm, but instead act to specify their ability to generate their progeny (neurons and glia). Because NBs still exhibit residual neurogenesis in the complete absence of ASC, we focused our efforts on identifying additional TFs that are expressed in the neuroectoderm and could act in parallel with ASC to impart the NB fate.

Tumour project:

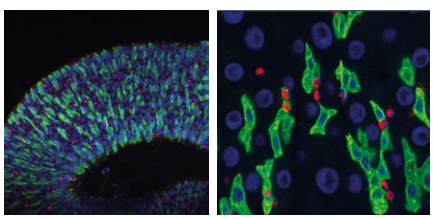
We continued our study of Notch-induced NB tumours in larvae, which we know arise from the de-differentiation of NB progeny. Upon allografting to adult hosts, these tumours spread throughout the body cavity and prematurely kill the host. We launched a single-cell RNAseq project (with Angela Giangrande, IGBMC, Strasbourg and Camille Stephan Otto-Attolini, IRB, Barcelona) to study the cellular diversity of the tumour. One surprising finding was that a subset of tumour cells can spontaneously differentiate into neurons. We also started studying a different tumour that arises from an epithelial cell type of the brain. Unlike the NB tumours, this epithelial tumour has a completely different histology and different molecular markers. It does not spread from the point of allografting, but still leads to premature death of the host.



A fragment of a T0 brain tumour (dsRed positive nuclei) is shown with a marker for neurons (white, also shown separately) and another for lactate dehydrogenase (green). Some neurons have extended axonal processes, whereas others seem still immature.

Gut project:

We have been studying the role of two chromatin regulators, Trx and E(z), in the biology of adult intestinal stem cells in collaboration with A. Eliopoulos (U. of Athens). We found that E(z) is crucial in maintaining the stem cells by keeping differentiation genes off (Veneti et al 2024). On the other hand, Trx seems to maintain the expression of an anti-proneural factor, which ensures the production of absorptive enterocytes, instead of neurosecretory-like eneteroendocrine cells (Fasoulaki et al 2025).



Wide view and close-up of adult intestines. Green marks the stem cells and their undifferentiated progeny. Red marks the nuclei of differentiated enteroendocrine cells.

Hey project:

In collaboration with Maria Monastirioti, we have been studying the Hes-like Hey TF gene, which (like Hes) is also a target of Notch, during asymmetric divisions of precursor cells in both the CNS and the midgut. We CRISPR-edited two putative enhancers of Hey, which resulted in complete loss of function, confirming that the basis of our enhancer prediction (Notch responsiveness via the Notch-tethering CSL TF) was correct (Monastirioti et al 2024).

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.

Web page: https://imbb.forth.gr/en/research/Christos-Delidakis.58/

Publications:

Veneti Z, et al. (2024) Polycomb-mediated silencing of *miR-8* is required for maintenance of intestinal stemness in *Drosophila melanogaster*. **Nat Commun.** 15(1):1924

Monastirioti M, et al. (2024) Notch-Dependent Expression of the *Drosophila Hey* Gene Is Supported by a Pair of Enhancers with Overlapping Activities. **Genes** 15(8):1071

Fasoulaki V, et al. (2025) Trithorax balances ISC fate decisions via Ptx1-mediated repression of EE specification. **bioRxiv** 2025.11.21.689716; doi: 10.1101/2025.11.21.689716

Anastasios Pavlopoulos

Principal Researcher

GROUP MEMBERS

Lab manager: Marina Ioannou
Postdoctoral researchers: Evangelia Stamataki, Miquel Sendra (Co-supervision with Dr. Léo Guignard, Institute of Developmental Biology of Marseilles, France)
PhD students: Maria Kalogeridi, John Rallis, Stylianos Svouros (Co-supervision with Dr. Dimitrios Sfyris, IACM-FORTH)
MSc students: Ioannis Liaskas, Dimitrios Papageorgiou, Sibora Teta
Undergraduate thesis student: Moschoula Chrousi
Research assistant: Kyriaki-Niovi Rafailidou
Visiting student: Emmanuela Veneri

EVOLUTIONARY DEVELOPMENTAL BIOLOGY & MORPHOGENESIS

Summary

The Developmental Morphogenesis Laboratory at IMBB-FORTH is an interdisciplinary group that brings together biologists, physicists, mathematicians and computer scientists to investigate how molecular, cellular and mechanical cues orchestrate the emergence of biological form through patterned cell activities. At the core of our mission is the development of cutting-edge genetic and genomic tools in the crustacean *Parhyale hawaiensis*, enabling us to move beyond descriptive analyses and to functionally test hypotheses about morphogenetic and physiological processes that are difficult or impossible to address in traditional model organisms. We combine these molecular and genetic approaches with advanced fluorescence microscopy and state-of-the-art image analysis pipelines to quantify morphogenetic events in live embryos at single-cell resolution, under both wild-type conditions and targeted genetic or mechanical perturbations.

Current aims

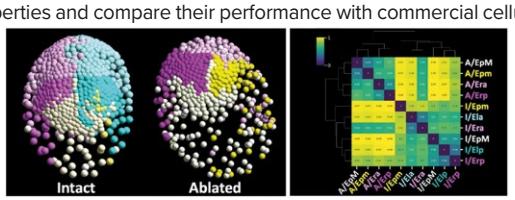
We use these integrated approaches to address several interrelated research questions:

1. How conserved and divergent are limb patterning and morphogenesis mechanisms across pancrustaceans?
2. What mechanisms drive cell packing, epithelial organization and remodeling during embryonic morphogenesis?
3. How are bilaterally symmetric tissue architectures established and restored during development?
4. What developmental mechanisms generate allometries among serially homologous limbs?
5. How do marine crustaceans achieve autonomous wood digestion in the absence of microbial symbionts?

Progress in 2024-2025

Many projects in our group have yielded significant insights into the patterning and morphogenetic mechanisms shaping animal form. The work summarized below has been completed or is nearing completion and is being prepared for publication.

1. We have combined functional genetics, genomics and bioinformatics to characterize the gene regulatory programs that drive limb specification and patterning in other arthropods outside in the insect model *Drosophila melanogaster*. We identified the enhancers that control the expression of the conserved patterning gene *Distal-less* (*Dll*) at different stages of limb development in *Parhyale*. Remarkably, despite more than 500 million years of independent evolution, the early-acting *Parhyale Dll* enhancer is also active in the limb primordia of *Drosophila* embryos. Parallel genetic studies in *Parhyale* and *Drosophila* have uncovered both conserved and divergent aspects of *Dll* regulation between direct developing (*Parhyale*) and indirect developing (*Drosophila*) limbs within pancrustaceans.
2. Animal epithelia typically exhibit honeycomb-like cell packing patterns characterized by the predominance of hexagonal cells. We investigated a striking deviation from this pattern in checkerboard-like square cell grids described in distantly related animals, including the ectoderm of crustacean species like *Parhyale*. By combining live imaging with quantitative image analysis, we showed that during ectoderm formation, cells transition from a hexagonal to a square packing pattern through the polarized shrinkage of specific cell junctions. Analyzing the dynamics of the contractile actomyosin cytoskeleton under wild-type and perturbed conditions, we found that square cell packing is mediated by the stalling of a widely conserved cell rearrangement mechanism, known as T1 transition.
3. In collaboration with computer scientists, we previously developed the first software solution (MaMuT) for cell tracking and cell lineage reconstruction from multi-dimensional and multi-terabyte image datasets. We have now created additional open-source software tools for the analysis of cell lineages. The first plugin (LineageTree) enables the computation of pairwise distances between cell lineages within and across embryos. The second plugin (ReLaX) allows the integration and interactive exploration of lineage information in the form of tree graphs, together with morphological and molecular genetic information represented as digital clones on 3D reconstructions of developing specimens at single-cell resolution.
4. As a distinct and final research direction, we investigated the cellulolytic cocktail produced by the digestive glands of *Parhyale* as a potential novel source of cellulases for biotechnological applications. Through an integrated strategy combining multi-omics analyses, functional genetics and biochemical assays, we dissected cellulase activity in vivo, overexpressed and purified individual *Parhyale* enzymes to evaluate their biochemical properties and compare their performance with commercial cellulases.



Reconstruction and comparison of cell lineages from intact and ablated *Parhyale hawaiensis* embryos, **Comparative Genomics Lab (CGLab)**

Other activities

- Teaching and academic service: I serve as lecturer and module coordinator, and as a member of the steering committees and the interview panels for three inter-institutional Master's programs in Molecular Biology and Biomedicine, Bioinformatics, and Biomedical Engineering.
- Mentorship: Members of the lab participated in international workshops and conferences, undertook research projects in collaborating labs abroad, and continued their studies in leading European universities and research institutes.
- Institutional responsibilities: I am an elected member of the IMBB Scientific Council, contribute to IMBB's Mentoring and Career Track Scheme and to EU-LIFE's Recruitment & Training Working Group, and serve as Science Communication Officer for IMBB's outreach and public engagement initiatives.
- Research Funding: We were awarded competitive grants from the Hellenic Foundation for Research and Innovation, Fondation Santé and the Theodore Papazoglou FORTH Synergy program.

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

Publications

Kalogeridi M, et al. (2025) Lineage tracing by light-sheet microscopy and computational reconstruction. **Methods Mol Biol** 2886:153-176
Cislo DJ, et al. (2025) "Morphogenetic Action" Principle for 3D Shape Formation by the Growth of Thin Sheets. **Phys Rev X** 15:021068

Alexandros Pittis

Assistant Researcher

GROUP MEMBERS

PhD student: Yannis Pyrris
MSc students: Amalia Kapsetaki, Kostis Paterakis, Eva Delidaki
Lab technician: Athena Marougka
Undergraduate thesis students: Melina Doudali, Asterios Tsiftsis

COMPARATIVE GENOMICS

Summary

We apply computational evolutionary approaches to disentangle the molecular basis of biological complexity. Our aim is to understand how protein families and cellular machinery evolved to create specialized functions, with particular focus on the emergence and diversification of nervous systems. We use rigorous phylogenetic analysis, integration of functional data, data analysis methodologies and selective experimental procedures, and seek to reveal fundamental principles that shaped cellular and neural evolution.

Current aims

The lab currently pursues interconnected research lines examining neural molecular evolution at multiple scales:

1. **Neurotransmission machinery evolution**: Tracing the origins of biogenic amine signaling systems and their transition from generalist to specialist machinery.
2. **Receptor system evolution**: Analyzing how receptor families (GPCRs, iGluRs) expanded across animal lineages, and exploring Protein Language Models for predicting protein interactions and functional properties.
3. **Cell type evolution**: Combining single-nucleus transcriptomics with evolutionary analysis to understand how neuronal cell types emerged in animals (HFRI-funded project starting 2026).
4. **Molecular basis of behavior**: Connecting cell-specific transcriptional signatures to behavioral phenotypes through collaborations.

Progress in 2024-2025

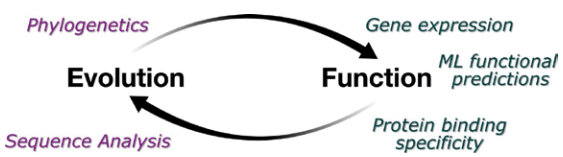
i) Following election as IMBB Researcher (November 2023), we established the Comparative Genomics Lab with renovated dry lab space and shared wet lab facilities. We successfully recruited and began training students at PhD, Master's, and undergraduate levels, and initiated collaborations with groups across IMBB and other FORTH institutes (Filiou at BRI, via a FORTH Synergy Grant on stress response transcriptomics).

ii) We demonstrated that biogenic amine neurotransmitter systems predate Bilateria. Through metabolomics, phylogenetic reconstruction, and functional receptor characterization, we showed these systems evolved from promiscuous ancestral enzymes and transporters toward specialized machinery via parallel gene duplications—representing a fundamental shift from paracrine to localized synaptic transmission. This work reframes our understanding of neural system origins and forms the basis for a major collaborative manuscript in preparation.

iii) A major HFRI-funded project led by PhD student Yannis Pyrris has established that fungi produce and store neurotransmitters in vacuoles or pump them extracellularly. Using integrated phylogenetics, genetic manipulation in *Aspergillus nidulans*, metabolomics, and functional transport assays, we characterized ancestral molecular systems that predate and gave rise to specialized animal neurotransmission. This work reveals unexpected conservation of neurotransmitter-handling machinery across the eukaryotic tree.

iv) We initiated systematic analyses of receptor family evolution. Work on vertebrate olfactory receptor evolution employs innovative Protein Language Model approaches for computational ligand prediction, and has advanced our understanding of the evolutionary forces that shaped the system. Parallel studies on ionotropic glutamate receptors have yielded new insights into NMDA channel family diversification across metazoans. Both projects are advancing toward publication.

v) We contributed to IMBB infrastructure development, including involvement in establishing the Bioinformatics Unit (core facility) and participation in the Institute's Data Management and Infrastructure planning.



Other activities

- Co-organized EMBO Lecture Course "Evolutionary and Comparative Genomics" in Nafplion, Greece (2024).
- Secured FORTH Synergy Grant with M. Filiou (BRI) on stress response transcriptomics.
- Secured HFRI grant "NeuroCompara" investigating neuronal evolution.
- Participating in Bioinformatics, Molecular Biology and Biomedicine, and Neurosciences MSc programs (University of Crete & IMBB-FORTH).
- Member of the IMBB Data Management and Infrastructure (DMI) planning group.
- Member of the IMBB Gender Equality Group (IGEG).
- PhD student Yannis Pyrris received FEBS funding for a 2-month research visit to EMBL, Heidelberg.

Web page https://cgenomicslab.org/

Publications

Ghasemi F., et al. (2025) Expansion, functional diversification and gene fusion events in the Ato protein family. **bioRxiv** 2025.05.26.656167

Gavriilidou A., et al. (2025) Advances and challenges in understanding evolution through genome comparison: meeting report of the European Molecular Biology Organization (EMBO) lecture course "Evolutionary and Comparative Genomics", **Bioinformatics Advances** 5(1): vbaf223

Nikos Poulakakis

Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Senior postdoctoral researchers: Argyro Nafplioti, Nikolaos Psonis
Research assistant: Eugenia Tabakaki
Lab technician & manager: Sevasti Koursioti
PhD students: Aggeliki Papadopoulou, Stefanos Papadantonakis, Maria Nefeli Choupa
Undergraduate thesis students: Ioannis Gonidakis, Catherine Chanioti
Collaborators: Pavlos Pavlidis (Collaborating Faculty Member, ICS-FORTH, Associate Professor, Department of Biology, UOC), Alexandros Stamatakis (Group Leader, Biodiversity Computing Group, ERA Chair, ICS-FORTH; Group Leader, Computational Molecular Evolution Group, Heidelberg Institute for Theoretical Studies, Germany; Full Professor, Institute for Theoretical Informatics, Karlsruhe Institute of Technology)

ANCIENT DNA PALEOGENOMICS & EVOLUTIONARY GENETICS

Summary

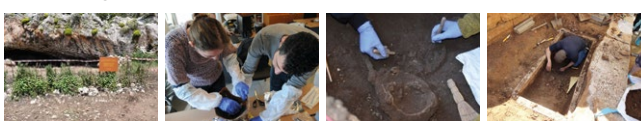
The Paleogenomics and Evolutionary Genetics (PEG) group (Ancient DNA Lab) at IMBB-FORTH is a nationally unique and internationally recognized research unit in ancient DNA (aDNA) and evolutionary genomics. Over the past seven years, PEG has established a strong network of international collaborations and has become the only archaeogenetics laboratory in Greece, as well as one of the most advanced in Europe. The mission of the group is to reconstruct evolutionary histories through the integrated analysis of ancient DNA, modern genomics, isotopic data, and bioinformatics, with a primary focus on human archaeology, zooarchaeology, and paleontology in the Eastern Mediterranean. Research interests include human evolution and population history, domestication and conservation genomics, extinct species, and the analysis of microbial DNA from sediments and ancient remains. Complementary isotopic analyses provide insights into past mobility, migration, diet, and palaeoenvironmental conditions. PEG has received funding from numerous competitive national and European programmes, implements pilot projects in collaboration with academic and research institutions, provides scientific services to the Ephorate of Antiquities of the Ministry of Culture, publishes in high-impact journals, and actively engages in public outreach activities.

Current aims

- Genetic profiling of Mesolithic hunter-gatherers to elucidate the population history of the Aegean.
- Study of Neolithic expansion and interactions between incoming and indigenous populations in the Mediterranean.
- Genomic analysis of culturally differentiated prehistoric and historical populations from Greek archaeological sites.
- Investigation of genetic relationships among medieval and post-medieval populations from Crete and mainland Greece.
- Reconstruction of the evolutionary history of extinct Mediterranean mammals.
- To investigate patterns of human occupation and cave use in prehistoric Greece through the analysis of sedimentary ancient DNA (sedaDNA) from cave deposits, while advancing and establishing sedaDNA methodologies and infrastructure in Greece in support of ERC Starting Grant preparation.

Progress in 2024-2025

1. **THESEUS project (2023–2025)** Implementation of the project "THESEUS: THe Genomics of the CrEtan population through hiStory and timE, shaping inflammation and immUne homeostasis", funded by the Hellenic Foundation for Research and Innovation under the National Recovery and Resilience Plan (Greece 2.0). The project aims to establish the Cretan Pan-genome through high-coverage whole-genome sequencing and functional analyses. To date, ~30X genomes from 119 individuals with local Cretan ancestry have been analyzed, and long-read PacBio HiFi sequencing has been completed for eight individuals from distinct regions of Crete. Manuscripts are in preparation.
2. **Spectra-Gen project (2023–2025)** Implementation of the "Spectra-Gen" project, funded by a Theodore Papazoglou FORTH Synergy Grant.
3. **International collaborations (2024–2025)** PEG leads or contributes to major collaborative projects with the University of Lausanne (ancient DNA analysis of skeletal remains from Euboea), the University of Geneva (Antikythera shipwreck archaeogenomic and isotopic analyses), Tel Aviv University (analysis of sedimentary ancient DNA from Greek caves, supporting ERC Starting Grant preparation), and McMaster University, Canada (targeted capture of Pleistocene elephants mitogenomes from the Eastern Mediterranean).
4. **Aegean Mesolithic project (2023–2025)** Finalization of a manuscript presenting the oldest genome sequenced to date from present-day Greece and the first Late Neolithic genomes from southern mainland Greece, providing new evidence for pre-Neolithic contacts with western Anatolia.
5. **Post-Byzantine Poros, Heraklion project (2023–)** Finalization of archaeogenomic analyses providing the first archaeogenomic data from the Christian, post-Byzantine cemetery of Poros (Heraklion, Crete) and the post-Byzantine cemetery of Doliani (Ioannina), addressing social dynamics and genetic affinities with other populations over time and space. The results indicate heterogeneous maternal and paternal lineages, absence of close biological kinship, and evidence for long-term population continuity and connectivity across the Aegean and Eastern Mediterranean.
6. **Pleistocene Cretan deer project (2025–)** Deep sequencing of promising deer samples from Pleistocene Crete that will shed light into extinct deer evolutionary history, taxonomy, and phylogeography, including the colonization of Crete and the subsequent radiation.



Training and other activities

PEG actively supervises PhD (Aggeliki Papadopoulou, Stefanos Papadantonakis, Maria Nefeli Choupa), and undergraduate students (Gonidakis Ioannis and Catherine Chanioti) from the University of Crete. Research visitors were hosted to strengthen methodological development and scientific output (**Aurora Campo, laboratory of Dr. Viviane Slon, in Tel Aviv University, Israel)**. Group members contribute to postgraduate teaching, invited lectures, and specialized training in ancient DNA methodologies (Nikolaos Psonis a) HAAM Summer School: Connecting the past, present, and future, 2025, 09 – 13 July, Human Ancient DNA, Ancestry, and Mobility community, Online event b) Invited talk on "Ancient Genomics: sample types, data, and tools to assess past biodiversity" at EMBO 2025 (24/05/2025) Satellite Workshop on Biodiversity Genomics, Heraklion, Crete, Greece and c) "Ancient DNA and applications in paleontology" in the context of the course "Modern Research Methods in Macropaleontology", (25/04/2024) Postgraduate M.Sc. Program of Paleontology-Geobiology, Geology Department, Aristotle University of Thessaloniki, Greece).

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

Publications Psonis N, et al. (2025) Genetic affinities between an ancient Greek colony and its metropolis: the case of Amvrakia in western Greece. Pre-print available in bioRxiv (07.2025), accepted to be published in **Genome Biology**

Bettisworth B, et al. (2025) Read Length Dominates Phylogenetic Placement Accuracy of Ancient DNA Reads**. Mol Biol Evol.** 42(2): msaf006

Psonis N, et al. (2024) Identification of the 18 World War II executed citizens of Adele, Rethymnon, Crete using an ancient DNA approach and low coverage genomes, **Forensic Science International: Genetics** 71:103060

Nektarios Tavernarakis

Professor / Medical School, University of Crete
–Collaborating Faculty Member

GROUP MEMBERS

Senior staff scientist: Maria Markaki
Lab manager / Special research assistant: Angela Pasparaki
Postdoctoral researchers: Stefania Kapsetaki, Georgios Konstantinidis, Dimitris Korovesis, Tereza Rubio-Tomás, Aggeliki Sotiriou, Dikaia Tsagkari
PhD students: Onur Cakıcı, Maria Fakitsa, Xuanyu Huang, Kostas Kounakis (2025), Thomas Madikas, Mrutyunjaya Panda, Dikaia Tsagkari (2025)
MSc students: Maria Kalykaki (2025), Eleftheria Panagiotidou (2025)
Undergraduate thesis students: Pavlos Kalitsounakis (2025), Konstantinos Papadopoulos (2025), Daphne Psaraki (2025), Antigoni Tzamtzi
Visitors and trainees: María Arrabal Ayala, LEFT IN 2025: Athanasios Fylaktakis, Georgia Karagianni, Nad'a Majerníková, Stavroyla Papadaki, Aggelos Papadimitriou, LEFT IN 2024: Elisavet Papa, Evangelia Papagrigoraki

NEUROGENETICS & AGING

Summary

We use the nematode *Caenorhabditis elegans* to investigate the molecular mechanisms underlying neuronal function and dysfunction. With its precisely defined nervous system comprising just 302 neurons, the worm offers a unique platform for dissecting neural processes at cellular and molecular resolution. Despite its minimal nervous system, *C. elegans* exhibits a rich repertoire of sensory capacities and behaviors. Such a wide spectrum of easily discernible phenotypes can be exploited using the sophisticated genetics and molecular biology tools developed for the worm. Building on these strengths, our studies focus on the molecular mechanisms of necrotic cell death in neurodegeneration and senescent decline, sensory transduction and integration by the nervous system, the interplay between cellular metabolism and ageing, and the development of novel genetic tools for *C. elegans* research.

Current work in the lab aims to:

1. Explore lipid metabolism – mitochondrial crosstalk in neuronal integrity and function during physiology and ageing.
2. Investigate the impact of the circadian clock on mitophagy and metabolism in Alzheimer's disease-associated neuronal degeneration.
3. Exploring the mechanisms by which metabolic reprogramming and *de novo* serine biosynthesis promote lifespan extension under conditions of mitochondrial protein import inhibition.
4. Examining the role of glial autophagy in neurophysiological processes and ageing using *in vivo* chemo-optogenetics.
5. Determine spaceflight-induced changes in gene expression and intracellular organization in *C. elegans* strains carrying genetically encoded organelle-specific markers.

Progress in 2024-2025

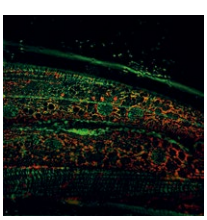
Our ongoing studies provide new insights into the role of nuclear hormone signalling in coordinating lipid and energy metabolism to preserve neuronal integrity and function. In this context, we have identified NHR-85 as a functional orthologue of peroxisome proliferator-activated receptor δ/β (PPAR δ/β), demonstrating that it modulates mitochondrial and lipid homeostasis to protect against α-synuclein aggregation in *C. elegans*. We continue to uncover novel modulators that govern the dynamic balance between opposing metabolic processes, including lipogenesis and lipophagy, as well as mitochondrial biogenesis and mitophagy.

Moreover, in collaboration with the University of Cologne, we recently established a novel germline-to-soma communication paradigm, showing that mitochondrial stress in the immortal germline activates the mitochondrial unfolded protein response (UPRmt) in the soma. These findings link the organismal response to mitochondrial stress to reproductive status, revealing that a decline in reproductive capacity is a primary cause of proteostasis collapse during ageing. Furthermore, we uncovered the sexually dimorphic nature of the UPRmt, demonstrating that male nematodes are inherently nonresponsive to this pathway.

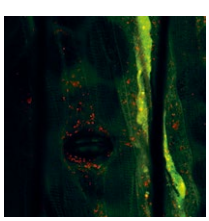
In collaboration with the research groups of Dr. Guido Kroemer and Dr. Frank Madeo, we elucidated the mechanism by which the natural polyamine spermidine enhances healthspan and lifespan across species under distinct regimens of fasting or caloric restriction. We found that spermidine levels increase during fasting in a range of model organisms, promoting hypusination of the translation factor eIF5A and thereby stimulating autophagy with associated lifespan and healthspan benefits. Overall, our study identifies the polyamine-hypusination axis as a phylogenetically conserved metabolic control hub that links fasting to enhanced autophagy and longevity.

Other activities

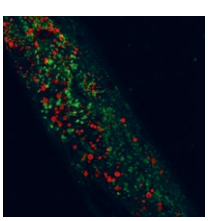
- Lecturer in Master's and Ph.D. programs in Greece and abroad. Mentor to Ph.D. students and postdoctoral researchers. Member of doctoral thesis committees across Europe.
- Awarded an Honorary Doctorate by Ionian University.
- Honored as a Distinguished Member of the Foundation for Research and Technology-Hellas (FORTH).
- Elected President of the European Molecular Biology Conference (EMBC).
- Honored with the Bodossaki Foundation, Excellence in Biomedical Sciences Award for his outstanding contribution to Biomedical Sciences.
- Co-organiser of international scientific workshops. Keynote and invited speaker at several international conferences.
- The group presented and contributed to international conferences and workshops (e.g., EMBO workshop: Cell Biology of the Nervous System: Cellular Mechanisms of Communication).
- The lab hosted the NT-5 PhD Conference on Drug Development for Alzheimer's Disease as part of the TClock4AD (Targeting Circadian Clock Dysfunction in Alzheimer's Disease) Marie Curie Doctoral Network.
- Members of the lab aquired prestigious positions to pursue their own independent labs in Greece (Dimitris Korovesis).



Live super-resolution imaging of nucleophagy in *C. elegans*



In vivo fluorescence reporter of autophagic flux in *C. elegans*



In vivo fluorescence imaging of intestinal lipid droplets (GFP) and lysosomes (LysoTracker Deep Red) in *C. elegans*

Web page www.elegans.gr/

Publications

Tavernarakis N. (2025) Phase separation meets energy generation to boost longevity. **Nature Aging**, 5: 1936-1938

Charmpilas N et al. (2024) Reproductive regulation of the mitochondrial stress response in *Caenorhabditis elegans*. **Cell Reports**, 43(6):114336

Hofer S.J., Daskalaki I., Bergmann M. et al. (2024) Spermidine is essential for fasting-mediated autophagy and longevity. **Nat Cell Biol** 26: 1571–1584

Maria Markaki

Senior Staff Scientist - Tavernarakis Lab

NEUROGENETICS & AGING

Physiological functions gradually deteriorate with age, increasing the risk of diseases such as neurodegenerative disorders. Although extensive research in model organisms has improved our understanding of ageing, the cellular and molecular pathways connecting ageing and neurodegeneration remain poorly understood. We are currently investigating how ageing affects autophagy and lipid metabolism and how alterations in these pathways may contribute to ageing and age-related diseases. We use the nematode *Caenorhabditis elegans* as a model organism to address these issues by combining genetics, genomics, molecular biology, and biochemical techniques with imaging approaches.

Other activities

- Lecturer in the advanced PhD course “ONE HEALTH: A Metabolic Approach from the Cell to Society, organized by the University of Coimbra. Provided academic guidance to undergraduate, master’s, and Ph.D. students and served on a doctoral committee at the University of Coimbra.
- Member of the Gender Equality, Inclusion and Diversity working groups of the IMBB and EU-Life (until October 2025).
- Member of the INCLUDE Project (Advancing Intersectional Gender Equality in Biomedical Research and Innovation), a Horizon Europe initiative addressing intersectional gender inequalities within biomedical research organisations.

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

Maria Monastirioti

Senior Staff Scientist in collaboration with Christos Delidakis group

NEURAL DEVELOPMENT

Neuronal cellular fate and function.

Our scientific interests focus on the biological processes and mechanisms underlying the determination of cellular fate and function within nervous system Using Drosophila as a model system, we have previously identified the bHLH-O protein Hey as a transcriptional target and effector of Notch intercellular signalling during the asymmetric division of progenitors within neuronal and intestinal tissues that generates two types of postmitotic cells with characteristic anatomical and functional properties. Further on, we completed a study on the characterization of two functional enhancers that contribute to the transcriptional control of the Hey gene expression in the CNS and the fly midgut elucidating their redundant role in supporting the Notch-dependent regulation of the gene. Currently:

a) we investigate the post-transcriptional regulation of Hey gene and the functional role of HeyTF in the determination of cell fates searching for its transcriptional targets.
b) We revive our interest on the insect neurotransmitter Octopamine, a Noradrenaline analogue that controls many physiological processes and behaviours in insects and in collaboration with Prof. Vontas group we pursue the generation and analysis of Octopamine deficient mosquitos with emphasis in their reproductive activity.

Recent publications: Monastirioti, M. et al. (2024) Notch-Dependent Expression of the Drosophila Hey Gene Is Supported by a Pair of Enhancers with Overlapping Activities. Genes 15: 1071. doi.org/10.3390/genes15081071

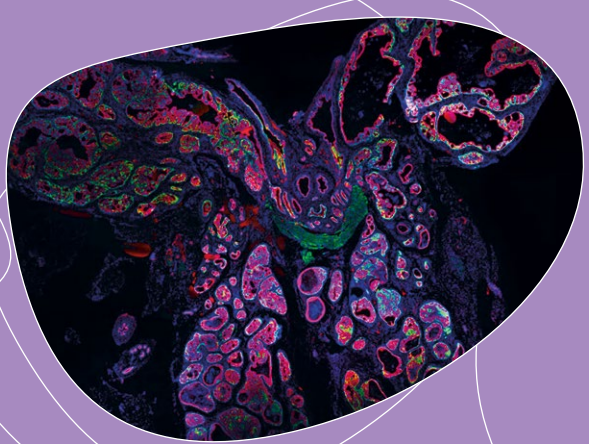
Kefi M. et al (2024) Insights into unique features of Drosophila CYP4G enzymes. Insect Biochemistry and Molecular Biology 164:104041doi.org/10.1016/j.ibmb.2023.104041

Other activities

- Lecturer in 4 courses oftwo Postgraduate Programs in ‘Neurosciences” (School of Medicine-University of Crete (UOC) and in “Molecular Biology & Biomedicine” (IMBB and Departments of Biology & Medicine (UOC)
- Training of graduate and undergraduate students.
- Member of the Office of Scientific Integrity at IMBB
- Main representative of IMBB in EU-LIFE alliance of European institutes.

Web page https://imbb.forth.gr/en/research/Maria-Monastirioti-Staff-Scientist.59/

Gene Regulation & Epigenetics



George A. Garinis

Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers: Georgina Chatzinikolaou, Callina Stratigi, Evi Goulielmaki, Athanasios Siametis, Giorgos Niotis
PhD students: Alexia Akalestou, Vivian Kalamara, Ermioni Arvanitaki, Ioanna Stavgiannoudaki, Manolis Theodorakis, Ilias Trygorniaris
MSc students: Katerina Boubouli, Nefeli Nikolarakou, Giorgos Chatzakis
Lab managers: Kavadina Katrakili, Konstantina Velanaki, Nikos Georgopoulos

GENOME INTEGRITY, DNA REPAIR, NEUROGENETICS & AGING

Summary

Our group investigates how genome instability drives inflammation, neurodegeneration, and systemic aging. Using genetically engineered mouse models carrying DNA repair defects or tagged DNA repair/transcription regulators, combined with functional genomics, single-cell approaches, and extracellular vesicle (EV) biology, we dissect how persistent DNA damage alters cellular homeostasis and contributes to age-related disease. Our work aims to define causative pathways that connect DNA repair, innate immune activation, neuroinflammation, and organismal decline, with the long-term goal of designing RNA- and EV-based therapeutic interventions.

Current aims

1. **Genome instability and immune activation in aging.**
   We investigate how DNA damage induces cytosolic DNA/RNA release, innate immune activation, and metabolic dysregulation across tissues. Using mouse models, primary macrophages and microglia, and in vivo EV tracking, we examine how DNA damage–driven inflammation shapes neurodegeneration, immunometabolism, and systemic homeostasis.
2. **DNA repair factors in mammalian development and disease.**
   Using cell type–specific knockout models and in vivo biotinylation tagging strategies, we study how nucleotide excision repair (NER) and transcription-coupled repair contribute to developmental gene expression, chromatin organization, and tissue-specific sensitivity to DNA damage.
3. **R-loops, transcription stress, and telomere biology.**
   Building on recent work showing that transcription-associated stress at telomeres triggers cytosolic DNA release and paracrine senescence, we analyze the mechanisms by which NER proteins, TOP2B, and chromatin regulators resolve R-loops to maintain genome stability and prevent inflammation.
4. **EV-based and RNA-based therapeutic interventions.**
   We develop engineered extracellular vesicles for targeted delivery of synthetic modified mRNAs encoding nucleases or RNA regulators to degrade cytosolic nucleic acids and suppress chronic inflammation. These studies support translational pipelines relevant to neurodegeneration and age-related inflammatory diseases.

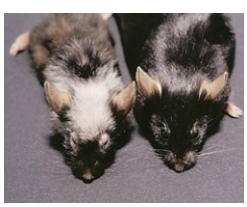
Progress in 2024-2025

- **Microglia-derived EVs and neurodegeneration:** Our group demonstrated that microglia release EVs carrying cytoplasmic DNA fragments that trigger neuronal cell death and age-related neurodegeneration upon DNA damage (PNAS 2024)
- **Telomeric transcription stress and paracrine senescence:** We uncovered that transcription stress at telomeres leads to cytosolic DNA release, driving paracrine senescence and inflammatory aging (Nat. Commun. 2024)
- **Nuclear antigen presentation & autoimmunity:** New findings demonstrate that DNA damage in macrophages drives immune autoreactivity via nuclear antigen presentation (Nature Aging 2025, in press)
- **Review & perspective leadership:** Contributions include major reviews on DNA damage in aging (Nat. Rev. Drug Discov. 2025) and on R-loop biology (FEBS Lett. 2024)
- **Advanced functional genomics:** Work from the laboratory and collaborators revealed TOP2B–XPF cooperation in R-loop processing (Sci. Adv. 2023) and DREAM complex regulation of DNA repair capacity (Nat. Struct. Mol. Biol. 2023)
- New Funding (2024–2025):
  - **RACE – ERA Chair Initiative for Ageing Research Excellence**, Horizon Europe (Coordinator; 2025–2030)
  - **InflaCare – ERA Chair Program to Advance Inflammation Research**, Horizon Europe (Coordinator; 2025–2030)
  - **TRIAD – Enhancing Synergies on Telomere Function in Health and Disease**, Horizon Europe (Coordinator; 2024–2027)
  - **Hevolution Foundation Award – Targeting Genome Stability as a Root Cause of Aging** (Co-PI; 2024–2028)
  - **National Precision Medicine Flagship Program on Alzheimer's and Parkinson's Disease** (Scientific Director; 2023–2025)

  These initiatives significantly expand the group's activities in aging, inflammation, neurodegeneration, EV therapeutics, and translational research.

Other Activities (2024–2025)

- Co-organizer: International Symposium on Genome Dynamics in Neuroscience and Aging (GDNA), Qingdao, China (2024)
- Co-organizer: EMBO Workshop on "Developmental Circuits in Aging", Nice (2024).
- Organizer: EMBO Symposium "The ageing genome: from mechanisms to disease", EMBL Heidelberg (2025).
- Key invited presentations (selected):
  - University of Cologne Aging Symposium (Keynote, 2025)
  - Extracellular Vesicles in the Nervous System, McGill/MNI (2025)
  - XP Meeting, Regensburg (2025)
  - EMBO YIP Genome Integrity Meeting, Istanbul (2024)
  - EMBO Workshop on Developmental Circuits in Aging, Nice (2024)
  - European DNA Repair Alliance (2024)
  - Groningen–Jena Aging Meeting (2023)



Animal models carrying congenital defects in DNA repair age in an accelerated manner

Web page https://imbb.forth.gr/en/research/George-A-Garinis.67/&tid=67

Publications

Arvanitaki ES, et al. (2024) Microglia-derived extracellular vesicles trigger age-related neurodegeneration upon DNA damage. **Proc Natl Acad Sci U S A**.121(17): e2317402121

Siametis A, et al. (2024) Transcription stress at telomeres leads to cytosolic DNA release and paracrine senescence. **Nat Commun.** 15(1):4061

Bujarrabal-Dueso A, et al. (2025) Targeting DNA damage in ageing: towards supercharging DNA repair. **Nat Rev Drug Discov.** 24(10):785-807

Dimitris Kardassis

Professor / Medical School, University of Crete
–Collaborating Faculty Member

GROUP MEMBERS

Senior research assistant: Paraskevi Papakosta
Postdoctoral researcher: Zouzana Kounoupa
PhD students: Isidoros Axiotis, Maria Laskou, Mariyanna Vinychaki
MSc students: Asimina Kakale, Kyriakos Nikolaou
Undergraduate thesis students: Despoina Lazaridou, Charalambos Karantonis
Exchange students: Veronika Vyletelova (University of Bratislava, Slovakia), Punnapa Thongsongkrit (Chulalongkorn University of Bangongk, Thailand)

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

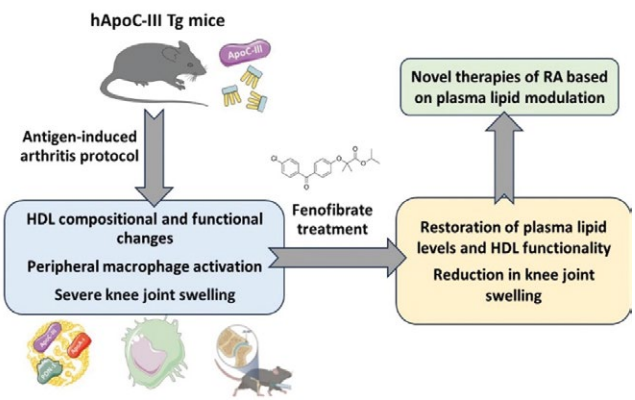
One major aim of our research is the understanding of the molecular mechanisms by which systemic dyslipidemia changes the metabolic phenotype of immune cells such as the macrophages and contribute to the pathogenesis of autoimmune diseases such as rheumatoid arthritis. A second aim is to understand the role of chronic inflammation on atherosclerosis and the functionality of High Density Lipoproteins. A third aim is to clarify the contribution of metabolic comorbidities on the pathogenesis of Alzheimer's Disease due to apolipoprotein E4 expression. A fourth aim is to develop 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 2024-2025

- We showed that high triglyceride (Tg) levels in mice change the metabolic profile of immune cells, compromises the anti-oxidant and anti-inflammatory capacity of High Density Lipoproteins (HDL) and aggravates knee swelling in a protocol of antigen-induced rheumatoid arthritis. Importantly, treatment of the mice with fenofibrate reduced Tg levels and significantly ameliorated arthritis severity.
- We showed that mice deficient in the apolipoprotein E (ApoE) gene, with high levels of total cholesterol, displayed a macrophage M1-like polarization and an increased respiration rate. Importantly, apoE KO mice developed more severe antigen-induced arthritis compared to control mice whereas treatment simvastatin limited the M1-associated cell surface markers on spleen macrophages and reduced arthritic joint swelling.
- Using targeted replacement mouse lines expressing human ApoE3 or ApoE4 we showed that dyslipidemia aggravated brain functions, especially in female mice, as measured by behavioral tests used in Alzheimer's Disease (AD). We also showed that purified recombinant ApoE4 can induce the expression of microglial TNFα gene and to transactivate the human TNFα promoter in BV2 cells confirming novel non-canonical roles of apoE in the microglial that could contribute to AD pathogenesis.

Other activities

- Member 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) (2023-2026)
- 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)
- Co-Editor of the Journal Atherosclerosis Plus (Elsevier)
- Member of the Organizing Committee of the 3rd Olympiad in Cardiovascular Medicine, Kalamata Greece April 30th-May 3rd, 2026
- Organizer of the Training School «Omics for Precision Medicine in ASCVD», September 16-18, 2024, Heraklion, Greece



Web page https://imbb.forth.gr/en/research/show/&uid=68&tab=142

Publications

Axiotis I, et al. (2025) Hypertriglyceridemia impairs HDL functionality, promotes macrophage metabolic activation and exacerbates antigen-induced rheumatoid arthritis in mice which can be reversed by fenofibrate treatment. **Biochim Biophys Acta Mol Cell Biol Lipids** 1870(8):159686

Mitić T, et al. (2025) Current status and challenges of multi-omics research using animal models of atherosclerosis. **J Mol Cell Cardiol Plus** 10;13:100476

Kardassis D, et al. (2025) Unravelling molecular mechanisms in atherosclerosis using cellular models and omics technologies. **Vascul Pharmacol.** 158:107452

Androniki Kretsovali

Emerita Research Director

Joseph Papamatheakis

Professor Emeritus – Collaborating Faculty Member

GROUP MEMBERS

Research technician: Takis Makatounakis
PhD student: Sirago Spanou
Undergraduate thesis students: Antzela Zgouro, George Dougalis, Amalia Christopoulou

GENE EXPRESSION AND CELL FATE REGULATION

Summary

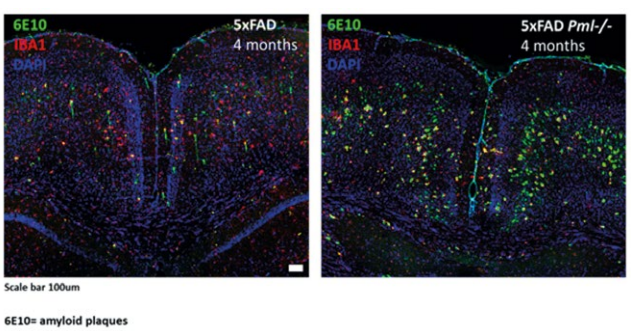
Our lab investigates the mechanisms by which transcriptional, epigenetic and signal transduction factors regulate cell fate. We have recently focused our interest on Promyelocytic Leukemia Protein (PML) a multitasking protein and organizer of the PML-NBs in embryonic and neuronal stem cells.

Current aims

1. **Role of PML in mouse embryonic stem cells (ESC) pluripotency**. Our previous work demonstrated that PML regulates ES cell–cycle progression and promotes both naïve and induced pluripotency. To elucidate the molecular pathways underlying these effects, we characterized the PML-dependent proteomic and SUMO-proteomic landscapes in ES cells.
2. **Role of PML in the nervous system**
   In the nervous system, PML has been implicated in brain development, circadian rhythm regulation, synaptic plasticity, and the degradation of misfolded proteins. Despite these associations, its role in neuro-inflammation and neurodegeneration remains largely unexplored.
   To investigate the contribution of PML to neural stem cell (NSC) physiology and stress responses, we analyzed E13.5 NSCs derived from wild-type and Pml$^{-/-}$ mice. Functional assays were integrated with transcriptomic and proteomic analyses.
   Given that PML-deficient NSCs display features reminiscent of neurodegeneration, we further explored a potential link between PML and Alzheimer's disease (AD) pathology using both the 5XFAD transgenic mouse model and an acute neuroinflammation model induced by intracerebroventricular (ICV) injection of β-amyloid (Aβ).
3. **Therapeutic strategies against Glioblastoma.**
   To explore therapeutic approaches for glioblastoma, we generated patient-derived cell lines and spheroids and treated them with a range of temozolomide and doxorubicin concentrations. In vitro findings were complemented by in silico predictive analyses.

Progress in 2024-2025

1. **Embryonic Stem Cells**. PML-dependent proteomic and sumoylomic analyses have provided key insights into the molecular mechanisms by which PML regulates embryonic stem cell (ESC) identity. We demonstrated that PML modulates pluripotency and cell-cycle progression by controlling the abundance and SUMOylation of critical regulatory factors. This approach identified SALL1 and CDCA8 as novel PML-directed SUMOylation targets, both essential for ESC maintenance. SUMOylation of SALL1 enhances Wnt pathway activation, thereby contributing to the suppression of ESC differentiation. Likewise, SUMOylation of CDCA8 increases its ability to promote cell proliferation.
2. **Embryonic Neural Stem Cells**. We showed that PML-deficient neural stem cells (NSCs) are significantly more susceptible to mitochondrial and amyloid-induced stress than control cells. Transcriptomic analyses revealed that PML loss compromises proteostatic and mitochondrial pathways. Specifically, we discovered that PML deficiency results in reduced autophagic flux and proteasome activity, leading to protein aggregate accumulation and stress-induced cell death. In addition, loss of PML disrupts mitochondrial integrity—evidenced by impaired respiration, reduced membrane potential, and altered mitochondrial morphology—likely driven by decreased PGC-1α expression and attenuated PPARγ signaling.
3. **Alzheimer's Disease Models**. Using an acute model of neuroinflammation 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. Furthermore, genetic ablation of PML in the 5XFAD mouse model revealed that loss of PML exacerbates multiple hallmarks of AD pathophysiology, including amyloid burden, neuronal toxicity, and cognitive decline.
4. **Therapeutic scheme against Glioblastoma.** Our findings indicate that a dual chemotherapeutic strategy combining temozolomide and doxorubicin effectively suppresses glioblastoma cell proliferation while enhancing cytotoxicity**.**



Loss of PML increases the amyloid depositions in 5XFAD mice. Representative brain sections from 4-month-old 5XFAD and 5XFAD Pml$^{-/-}$ mice were immunostained with 6E10 (amyloid), Iba1, and DAPI.

Other activities

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

Web page: https://imbb.forth.gr/en/research/Androniki-Kretsovali.69/ https://imbb.forth.gr/en/research/Joseph-Papamatheakis.76/

Publications

Spanou S, et al. (2025) PML is crucial for neural stem cell differentiation, stress tolerance and mitochondrial integrity. **Stem Cell Reports.** 20(9):102598

Spanou S, et al. (2025) Protein (PML) Regulates Stem Cell Pluripotency Through Novel Sumoylation Targets. **Int J Mol Sci.** 26(3):1145

Oraiopoulou ME, et al. (2024) The Temozolomide-Doxorubicin paradox in Glioblastoma in vitro-in silico preclinical drug-screening. **Sci Rep.** 14(1):3759

Matthieu Lavigne

Assistant Researcher

GROUP MEMBERS

Research assistants: Electra Tsaglioti, Dimitris Tzanos
Postdoctoral researchers: Ourania Galanopoulou
PhD student: Vaios Theodosiou
MSc students: Marianna Stagaki, Nikolaos Vouzounerakis, Konstantinos Tsomakian, Aggeliki Loukoupolou, Angelos Papadimitriou, Antonia Chairetaki
Undergraduate thesis students: Maria-Electra Kontonikou, Stergios Manakas, Christos Botos, Aikaterini Ntouka, Ourania Koukaki, Pelagia Stefanaki

GENE CONTROL MECHANISMS

Summary

The mission of the group is to model and understand novel (co-)transcription regulatory mechanisms associated with nascent RNAs (nRNAs) transcribed by RNA polymerase II (Pol 2). How do they impact chromatin state and genome function? It is necessary to characterize how RNA-rich Transcription Loops (TLs) formed by transcribing Pol2 synthesizing voluminous nascent ribonucleoprotein particles (RNPs) impact the 3D interactome of harboring genomic loci. We test how cancer cells enable global elevated levels of mRNA that sustain their rapid growth and survival. We are combining state-of the art genome engineering and chromatin biology approaches with an innovative systems biology approach relying both on multi-omics and mathematical modeling. Rates of initiation, proximal promoter pausing, elongation and co-transcriptional splicing are estimated via virtual or real perturbation schemes that influence transcriptional output (e.g. genetic, pharmacological, environmental) in modeled molecular networks. Our strategy infers transcriptional/epigenetic principles and discover steps that are crucial for proper transcription, splicing, epigenome regulation and DNA repair (Liakos et al., 2025) and can identify disease-enabling components of the system that open new avenues for therapeutics.

Current aims

We investigate how nRNAs interact with chromatin components to regulate transcription and epigenome. RNF20/40 that ubiquitinates histone H2B is an essential complex in hepatocarcinoma cell lines where its depletion correlates with highly deleterious effects on cell survival. Co-transcriptional splicing can change abundance of RNF20/40 in the vicinity of transcribing Pol 2 around intron-exon junctions (Figure a-b). We therefore propose that interactions between nRNA and chromatin feedback on splicing accuracy and ask if condensates formation confers physico-chemical robustness to the system.

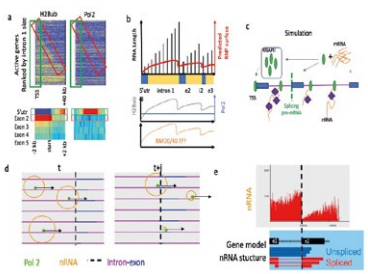
In parallel we test neoepitopes expression in cancer after genotoxins challenge of transcription and measure aberrant co-transcriptional splicing. We want to push cancer cells to be recognised as 'foreign' by the immune system and improve immune-checkpoint inhibitors (ICI) strategies (Palli et al, 2025).

Our interdisciplinary collaborative (IMBB, IACM, IESL) approach combining wet lab experiments (e.g. genome engineering, microscopy, NGS methods, biochemistry) with advanced bioinformatics (epi-genomics and transcriptomics analyses) and mathematical biology (e.g. in-silico simulation, Machine Learning, dynamical systems) aims to mimic biological processes and improves our capacity to interpret the biological meaning of the multiparametric nature of our multimodal results.

Progress in 2024-2025

The effect of nascent RNA on chromatin relies on interactions between chromatin factors and Pol2 and nRNAs that regulate Pol 2 elongation rate and processivity and RNA splicing. We generated a mutant human hepatocellular carcinoma cell line by CRISPR-Cas9 technology where we tagged and enable acute depletion of RNF20/40 (dTAG). We are applying/developing new tools (e.g EU-seq, FISH, IF, bioinformatics analyses of GRID-seq data) that enable us to study what exact changes in nRNA-related chromatin composition and interactions occur. We mapped H2Bub and RNF20/40 (ChIP-seq) and focused at splicing sites to show how inhibition of splicing impedes proper localization and levels of H2Bub. We also correlated nRNA production rate and patterns (nRNA-seq, splicing analysis) to effects on H2Bub.

Finaly, we implemented computational modeling of transcription dynamics by simulation optimization (Figure c-d) to model Gene regulatory networks (GRNs) that control global or specific gene expression in heath or disease. With Machine learning (ML) models that exploit prior knowledge ground-truth information (from experimental data), we can infer with good accuracy what are the most influential steps controlling pol II dynamics and nRNA synthesis/ splicing rates (Figure e) and predict system's sensibility to various drugs or KO experiments. In the future, we want to integrate our framework to single-cell multiomics pipelines where we have inferred Setdb1-driven gene regulatory rules that control differentiation of adult intestinal stem cells in mouse intestinal (Peraki et al., 2025).



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

- Scientific head of the IMBB Genomics Facility
- Lecturer and coordinator of Omics and Bioinformatics courses in the MSc Program in "Molecular Biology and Biomedicine" and in "Bioinformatics" of the University of Crete and IMBB-FORTH
- Awarded a HORIZON WIDERA TWINING grant in 2024 with Pr Delidakis and Dr Theodorou (IMBB) to improve single-cell Omics and Bioinformatics capacities in IMBB
- PhD student Vaios Theodosiou received a PhD fellowship in 2025 from HFRI
- Partner lab in the BrainPrecision Flagship action (2023-25)
- Seminar at BRI-FORTH Ioannina (Online): "Codes for decoding mechanisms of gene regulation and maintenance" (14/03/2025)
- Selected talks at the HSBMB and HSCBB conferences "Mechanistic Insights into Transcription Dynamics Uncovered by In Silico Simulation and Mathematical Modeling"

Web page https://imbb.forth.gr/en/research/Matthieu-Lavigne.70/ https://pubmed.ncbi.nlm.nih.gov/?term=Lavigne+MD&sort=date

Publications

Peraki I, et al. (2024) Setdb1 safeguards proper differentiation of adult intestinal stem cells by controlling chromatin accessibility and transcriptome variability. **bioRxiv**, 2024.10.18.619079

Palli E, et al. (2025) Transcriptomic signatures in peripheral CD4+Tlymphocytes may reflect melanoma staging and immunotherapy responsiveness prior to ICI initiation. **Frontiers in immunology** 16:1529707

Liakos A, et al. (2025) Cockayne syndrome B protein is implicated in transcription and associated chromatin dynamics in homeostatic and genotoxic conditions **Aging Cell** 24(1):e14341

George Mavrothalassitis

Professor / Medical School, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

PhD student: Aikaterini Vourlia
MSc student: Irini Vassilaki
Undergraduate thesis students: 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

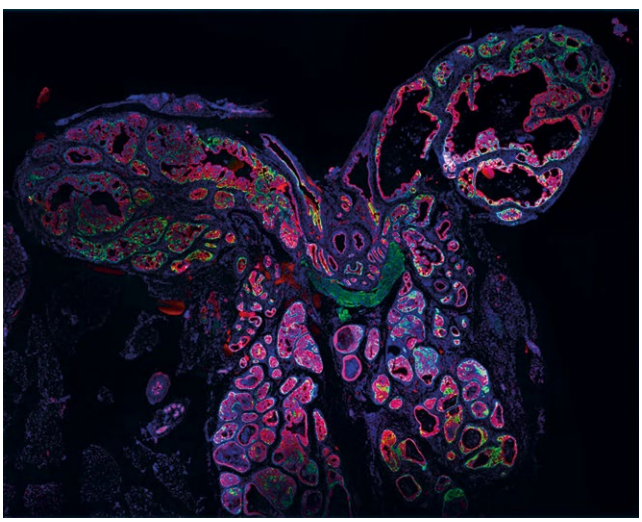
Our goal is to decipher the contribution of the ubiquitously expressed, Mapk-regulated transcriptional repressor ERF in development and disease and explore its potential as a therapeutic target. Erf defects have been shown to lethally affect placenta and hematopoietic embryo development, and lead to syndromic craniosynostosis, Chitayat syndrome, MIDES syndrome, Noona-like syndrome, prostate cancer, Ewing's sarcoma and other pathologies. 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 2024-2025

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. We developed reporter prostate cell lines to explore the pharmacological induction of ERF cellular activity in prostate cancer. We identified ERF as the causing factor in the newly myoskeletal and neuronal MIDES syndrome.

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. FORTH representative in the HFRI general assembly. Member of the IMBB bridging committee. Member of the IMBB OSI committee.



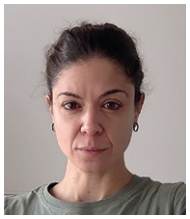
Confocal image of whole mouse prostate from a double KO castrated animal, showing extensive basal and luminal adenocarcinomas. Stained for luminal (red) and basal (green) epithelial cells and nuclear DNA (blue).

Web page https://www.imbb.forth.gr/en/research/George-Mavrothalassitis.71/

Publications

Baltsavia I, et al. (2024) scRNA-Explorer: An end-user online tool for single cell RNA-seq data analysis featuring gene correlation and data filtering. **J Mol Biol.** 436(17):168654

Lucia Micale L, et al. (2025) Heterozygous variants disrupting the interaction of ERF with activated ERK1/2 cause microcephaly, developmental delay and skeletal anomalies. **Eur J Hum Genet.** 33(6):718-726



Evgenia Ntini

Principal Researcher

GROUP MEMBERS

PhD students: Christos Katsioulas (H.F.R.I Fellow), Angelos Kozonakis
MSc students: Maria Ilektra Kontonikou, Stavroula Papadaki

EPIGENETICS, RNA BIOLOGY & GENE REGULATION

Summary

Research in our group is focused on understanding mechanisms of co-transcriptional RNA processing, with a focus on RNA-binding proteins underlying the processing and biogenesis of long non-coding RNAs (lncRNAs) in regulation of gene expression, in health and disease contexts. Our vision is to leverage delineated basal molecular mechanisms in RNA biology, combined with applied bioinformatics, transcriptomics and multi omics data integration, so that our research projects converge towards RNA-based therapeutics, informed by machine/deep learning and predictive modeling.

Current aims

Through multi omics data integration from large clinical cohorts and machine learning, we recently unraveled the impact of co- and post-transcriptional processing of a chromatin-associated lncRNA in shaping gene expression, acting on a micro-RNA (miR-200) regulatory axis [preprint 1]. We aim to further dissect mechanistic details of this mode of regulation by uncovering specific nuclear and chromatin-associated residing RNA-binding protein interactions of this lncRNA and alike transcripts in breast cancer cells. By leveraging established pipelines in our lab including CRISPR artificial splicing modulation and long-read sequencing, we aim to characterize the roles of lncRNA alternative splicing isoforms in gene regulation. Finally, with a support of a H.F.R.I grant, we set off to uncover mechanistic roles of nascent RNA modifications in splicing regulation during cell differentiation.

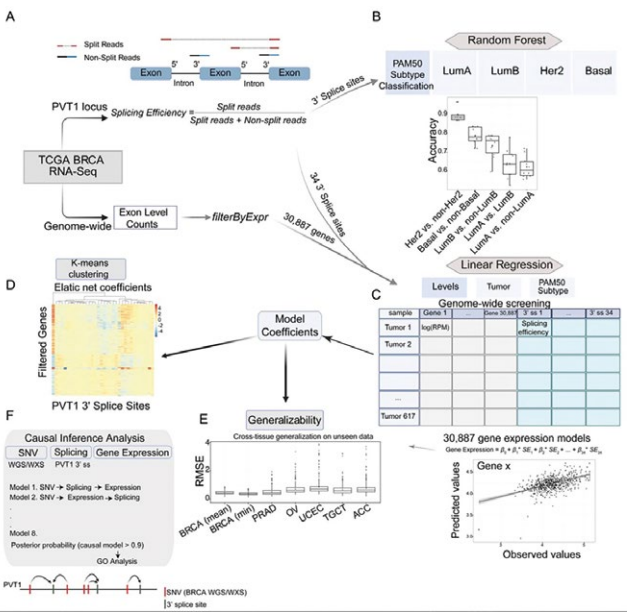
Progress in 2024-2025

- We established bioinformatic analyses for the integration of TCGA data in machine learning models to characterize the role of lncRNA splicing in gene regulation in breast cancer context and experimentally validated the predictive models via artificial splicing modulation in vitro (Kozonakis et al. submitted, bioRxiv preprint; Figure 1).
- In collaboration with the Chachami lab (UoTh), we contributed transcriptome-wide analyses of omics data to uncover transcriptomic and splicing alterations in response to hypoxia[1].
- In collaboration with L. Schulte (Uni Marburg), we contributed bioinformatics analyses to reveal the role of lncRNAs in shaping immune response-related transcriptional networks[2].

Our research has been funded by a Fondation Santé Research Grant, an H.F.R.I. PhD fellowship to C. Katsioulas, and an H.F.R.I. Research grant to E. Ntini (NAREPIC #24867).

Other activities

- Supported by an RNA Society grant, we organized monthly RNA salons with invited speakers (Twitter@CretanRna)
- The PI participated as a mentor in the EU-LIFE Mentorship programme.
- The PI was an invited speaker at Dagstuhl Seminars on Deep Learning for RNA Regulation and Multidimensional Transcriptomics (Germany, 2024).
- The PI received a Biochemical Society Travel Grant for giving a talk at the Eukaryotic RNA turnover meeting (UK, 2025).



Web page https://imbb.forth.gr/en/research/Evgenia-Ntini.72/

Publications

Filippopoulou C, et al. (2024) Hypoxia-driven deSUMOylation of EXOSC10 promotes adaptive changes in the transcriptome profile. **Cell Mol Life Sci.** 81(1):58

van den Berg van Saparoea ACH, et al. (2024) Plasmid Delivery and Single-Cell Plasmid Expression Analysis for CRISPR/dCas9-Based Epigenetic Editing. **Methods Mol Biol.** 2842:255-265

Schmerer N, et al. (2025) A searchable atlas of pathogen-sensitive lncRNA networks in human macrophages. **Nat Commun.** 16(1):4733

Charalampos Spilianakis

Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Special research assistants: Manuela Kapsetaki, Deppie Tsoukatou, Panagiotis Papadopoulos
PhD students: George Papadogkonas, Dionysios-Alexandros Papamattheakis, Polina Gkoublia, Harish Kalaiarasan
MSc students: Eirini Kokolaki, Webby Prendi, Eleftherios Morres
Undergraduate thesis students: Marina Kalaitzaki, Charitomeni Stamatiadi

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. Through this multidisciplinary approach, the lab aims to reveal fundamental principles of genome organization that underlie immune cell development, function and disease.

Current aims

A major aim of the lab is to understand how high-order chromatin organization regulates T-cell differentiation and function and how its disruption contributes to autoimmunity. We investigate the role of 3D chromatin architecture in transcriptional control, focusing on key genome organizers such as CTCF and Special AT-rich Sequence Binding Protein 1 (SATB1), particularly during T-cell development and immune activation.

The lab also studies non-coding RNA-dependent regulation of the immune system and how nuclear architecture influences genome activity. This includes examining spatial positioning of gene loci, enhancer networks and chromatin loop dynamics and how their alteration can drive immune-mediated pathology. We employ advanced mouse models, next-generation sequencing, imaging (including super-resolution microscopy) and computational/biophysical modeling to dissect epigenetic mechanisms that control immune responses.

Progress in 2024-2025

An outstanding question in immunology is how chromatin is organized in 3D, which factors establish or maintain this loopscape and how these organizational principles shape gene-regulatory pathways that support (patho)physiological processes. During 2024 and 2025, the Spilianakis Lab continued to contribute to this field by integrating single-cell and 3D genome approaches to connect nuclear architecture with immune cell fate decisions. Our work further highlighted how genome organizers and chromatin-associated factors cooperate with transcriptional and epigenetic programs to fine-tune T-cell differentiation and immune homeostasis.

Key advances in this period include:

i) mechanistic dissection of SATB1-dependent chromatin nano-domains and their coupling to active transcriptional hubs;
ii) clarification of how 3D enhancer connectivity supports stable T-cell lineage decisions; and
iii) translation of these principles to autoimmune settings, including lupus-related inflammatory pathways.

These studies reinforce the lab's central theme: that higher-order genome organization is not merely structural, but a causative epigenetic layer governing immune cell identity and disease susceptibility. Overall, the biennium strengthened the lab's bridge between fundamental genome biology and clinically relevant immune dysregulation.

Other activities

Invited speaker at the University of Limoges, October 03-06 2024. Disseminating the lab's activities by delivering two talks to the lay audience, one in Heraklion December 13 2024 as part of "Biology in Town" ("*What we are is defined by our genes or our environment?*") and one in Rethymnon April 30 2025 as part of the "Ecology Nights" ("*From classic Genetics to Epigenetics*").

In parallel, the lab actively contributed to national and European collaborative research initiatives and consortia in immunobiology and chromatin/epigenetics, strengthening IMBB-FORTH visibility and cross-disciplinary partnerships.

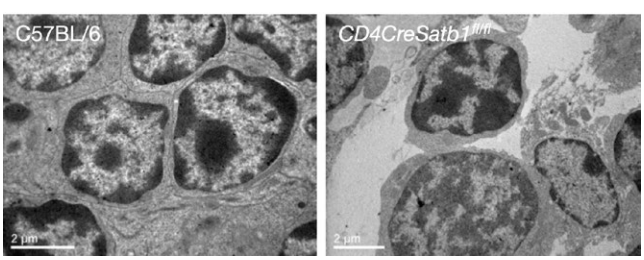


Figure Legend
Transmission Electron Microscopy images of wild type and Satb1 conditional knockout mouse thymi, showing disrupted thymic architecture associated with autoimmunity.

Web page https://imbb.forth.gr/en/research/Charalampos-G-Spilianakis.73/

Publications

Spilianakis C, (2025) Quiet custodians of $CD8^+$ T-cell fate. **Nat Immunology** 26: 2122–2123

Kosmara D, (2025) SMC1A, a sex-biased chromatin modifier, acquires specific regulatory function in lupus shaping inflammatory pathways that promote autoimmunity. **Nat Commun.** 16(1):10350

Constantine A. Stratakis

Professor / University of Athens Medical School –Collaborating Faculty Member

GROUP MEMBERS

Principle Staff Scientist: Dr. Emmanouela Linardaki
Postdoctoral researchers: Evmorfia Tzagkaraki, Elena Vorgia, Dionysia Petratou, Rodanthi Lyraki
Research Assistant (MSc): Polymnia Gkoumplia (Bioinformatics)
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)

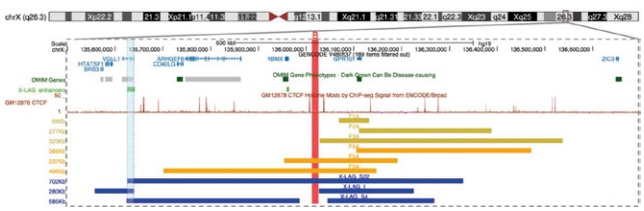
Current aims

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 2024-2025

- We assisted in the development of mouse models of the PKA pathway.
- We identified *in silico* potential GPR101 ligands.
- Novel molecular aspects of Cushing syndrome were published.
- A novel disease was described, caused by activating $G_{\alpha i2}$ mutations in patients with impaired immunity and endocrine disorders, among other phenotypes
- DIGENIA and EDIMO run hundreds of human samples for genetic testing.
- DIGENIA received funding to participate in the Health Hub project (https://healthhub-edih.eu/)



GPR101 is a G protein-coupled receptor (GPCR) implicated in a rare form of genetic gigantism known as X-linked acrogigantism, or X-LAG. Overview of genomic duplications at the chromosome Xq26.3 locus involving *GPR101*. The genomic region surrounding *GPR101* is shown with annotated protein-coding and OMIM genes (blue and dark green, respectively), CTCF binding sites (orange ChIP-seq track from GM12878 cells), and two putative CREs located within an intron of *VGLL1* and the promoter region of *RBMX* (light green bars). The centromeric TAD boundary is marked by a red vertical bar. Colored bars below represent the extent of individual duplications: yellow for three non-pathogenic duplications previously reported, orange for the three newly identified non-pathogenic duplications presented in this study, and blue for known representative X-LAG-associated pathogenic duplications, including both continuous and discontinuous rearrangements. Only pathogenic duplications span the *VGLL1* intronic enhancer, highlighted by a light blue vertical bar. All non-pathogenic duplications, despite partial TAD disruption or inclusion of other CREs such as the *RBMX* enhancer, were predicted by POSTRE to be neutral. (from **NPJ Genom Med. 2026** Jan 15. doi: 10.1038/s41525-025-00548-7).

Other activities

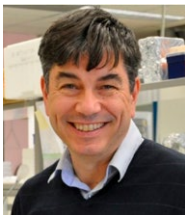
- EDIMO received the 2025 Healthcare Business Gold Award for Development & Innovation (https://edimo.gr/vravefsi-tou-edimo-sta-healthcare-business-awards-2025/)
- Dr. Constantine Stratakis received the 2024 AHEPA Award for his contributions to Research and Development in Greece and the 2025 Athens Rotary Award for his contributions to Medicine and Innovation.
- Dr. Constantine Stratakis was selected to serve as Professor of Pediatrics at the Medical School of the University of Athens, Greece (May 2024) https://2-pediatric.gr/iatroi/endokrinologiko-iatreio/konstantinos-stratakis/

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

Publications:

Bouys L, et al. (2025) KDM1A genetic alterations, a rare cause of primary bilateral macronodular adrenal hyperplasia, strongly associated with food-dependent Cushing's syndrome: results of its systematic germline screening in 301 index cases and genotype/phenotype correlation. **Eur J Endocrinol.** 192(2):119-127

Ham H, et al. (2024) Germline mutations in a G-protein identify signaling crosstalk in T cells. **Science** 385(6715): eadd8947



Iannis Talianidis

Research Director, AXA Chair

GROUP MEMBERS

Post-doctoral researchers: Orsalia Hazapis, Haroula Kontaki, Marina Koukaki, Effie Thymiakou

PhD students: Dimitris Botskaris, Ourania Galanopoulou, Ioannis Giannoulakis, Evaggelia Tachmatzidi, Athina Tavernaraki

CHROMATIN & CANCER EPIGENETICS

Summary

The main interest of the group is to understand basic transcription regulatory mechanisms and the identification of novel epigenetic mechanisms, which control hepatic gene expression. Special emphasis is placed on the elucidation of the role of these mechanisms in liver development, in normal and pathological metabolic homeostasis and in liver cancer development.

Current aims

We studied the mechanism of developmental activation of hepatic genes, with particular focus on dynamic changes of 3D genome organization during development. We have also investigated the the role of Setdb1 function in intestinal progenitor cells in heterochromatin maintenance and cell-to-cell transcriptome variability in cellular diversification during differentiation. In addition, we have developed and analyzed new genetic mouse models, devoid or overexpressing epigenetic regulators to gain deeper insights into the mechanism of transcriptional addiction of cancer, characterized by increased global nascent transcription rates.

Progress in 2024-2025

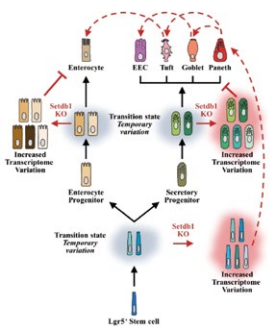
We performed chromosome painting, HiC and promoter-capture HiC experiments in different developmental stages to investigate the contribution of the different layers of 3D genome organization (i.e., chromosome positioning in nuclear territories, folding into multimegabase-sized A/B compartments or in sub-megabase level Topologically Associated Domains (TADs) and the formation of Loop domains within TADs and Enhancer-Promoter contacts) in the establishment of stage-dependent gene expression patterns during mouse liver development. The results revealed that all organizational layers are dynamically changed during development and each of them contribute to developmental gene activation. In line with this, we found that the formation of enhancer-promoter complex through cohesin-mediated loop extrusion determines the developmental timing of activation of hepatic genes. The results also suggest that cohesin complex may play an active regulatory role in transcription elongation.

The potential contribution of chromatin modifications associated with cancer-specific elevated transcription elongation rates was evaluated by studying the role of gene body H2BK120Ub modifications using Usp22-KO and Usp22 overexpressing Tg mouse models in experimentally-induced liver cancer. We observed a protective effect of Usp22 inactivation in the development of DEN-induced liver tumor formation. Our data demonstrate that Usp22 and gene-body H2B ubiquitination influences RNA Polymerase-II pausing and release, which is part of the complex mechanism responsible for the elevated global transcription rates in cancer. The human relevance of the finding was demonstrated in patient-derived human liver cancer organoids.

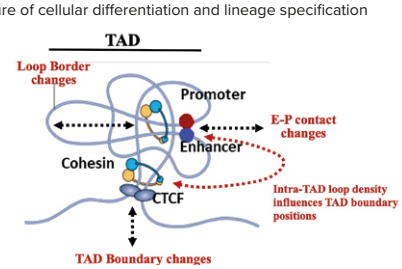
Setdb1 is a major H3K9 methylase involved in heterochromatin maintenance. Our study using conditional Setdb1-KO model, inactivating Setdb1 specifically in Lgr5+ intestinal stem cell, demonstrated its pivotal role in intestinal stem cell differentiation by fine-tuning chromatin accessibility in open euchromatin regions through which it controls transcriptional variability between cells. Importantly, the study revealed relatively uniform transcriptomes at each consecutive differentiation state, which are preceded by a transition period, displaying highly variable transcriptomes. The increased cell-to-cell transcriptome variability provides multiple choices for cellular diversification.

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.
- Presentations in AXA Research Fund events and other international workshops.



Transient increase of cell-to-cell transcriptome variations at the transition periods represents a hallmark feature of cellular differentiation and lineage specification



TAD boundaries and Loops are extensively reorganized during liver development. The density of the Enhancer-promoter contacts within loop domains and TADs influences their boundary positions.

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

Publications

Galanopoulou O, et al. (2024) Endonucleosis mediates internalization of cytoplasm into the nucleus. **Nat Commun.** 15(1):5843

Peraki I, et al. (2024) Setdb1 safeguards proper differentiation of adult intestinal stem cells by controlling chromatin accessibility and transcriptome variability. **BioRxiv version**: doi: https://doi.org/10.1101/2024.10.18.619079

Papanastasatou M, et al. (2025) Dual regulatory role of natural killer T cells during development of hepatocellular carcinoma. **Commun Biol.** 8(1):1478

Manolis Pasparakis

CECAD, University of Cologne

Adjunct Researcher, ERA Chair IMBB-FORTH

GROUP MEMBERS

Postdoctoral fellows: Georgina Chatzinikolaou, Evi Goulielmaki, Callina Stratigi
PhD students: Ilias Trygoniaris, Katerina Zacharopoulou, Manos Theodorakis)
Technician: Nikos Georgopoulos

INFLAMMATION BIOLOGY & IMMUNITY

Prof. Manolis Pasparakis joined IMBB-FORTH as ERA Chair to establish a dedicated program on inflammation research and immune-mediated disease mechanisms.

Prof. Pasparakis is internationally recognized for pioneering discoveries on how programmed cell death pathways regulate inflammation and tissue homeostasis. His research revealed that aberrant activation of innate immune signalling triggered by cellular damage or endogenous nucleic acids drives autoimmune disease, cancer, and chronic inflammatory pathology. The Pasparakis research program at IMBB investigates how genome damage activates innate immune sensing and drives inflammatory disease, with the aim of translating these insights into therapeutic strategies. It focuses on Toll-like receptor signalling, cytosolic DNA/RNA sensing pathways (cGAS–STING, RIG-I/MDA5), type I interferon–mediated autoinflammation, inflammation in cancer and regeneration, and RNA-based interventions targeting pathogenic nucleic acid sensing.

The ERA Chair project establishes an interdisciplinary inflammation research hub that integrates mouse genetics, omics technologies and translational therapeutic development to identify novel biomarkers and intervention strategies for inflammatory and autoimmune diseases. InflaCare will implement clear, measurable objectives to strengthen IMBB's position by creating a dedicated platform around the ERA Chair and team, expanding research capacity and competitiveness, enhancing training and mobility, attracting talent, reinforcing industry engagement, upgrading administrative and grant management structures, leveraging EU and national infrastructures, and increasing visibility and societal impact.

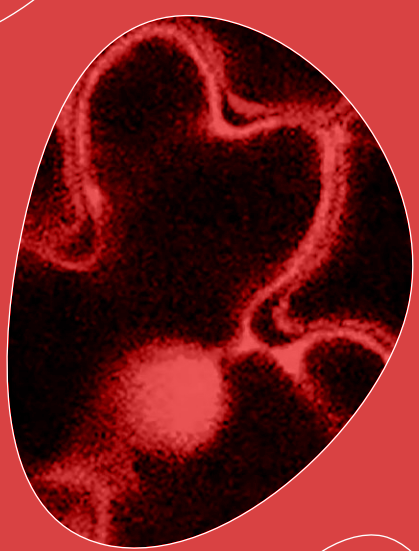
Research strategy:

The group investigates how endogenous nucleic acids released after cellular damage activate innate immune receptors and trigger pathological inflammation. Particular emphasis is placed on TREX1, ADAR1 and related pathways that prevent aberrant interferon responses. Genetically engineered mouse models combined with single-cell transcriptomics, proteomics and metabolomics are used to study disease mechanisms in vivo. A translational arm develops RNA-based therapeutic strategies aimed at eliminating cytosolic nucleic acids using synthetic modified mRNAs encoding nucleases. Targeted nanocarrier delivery is explored for treatment of interferonopathies and neuroinflammatory disorders.

First-year progress:

InflaCare is now fully operational. The ERA Chair holder has been successfully integrated into IMBB structures, and the research team has been recruited and established on site. Key animal models have been imported and are being maintained in the IMBB facility, enabling the immediate launch of the core research themes on inflammatory signalling and nucleic acid sensing. Experimental platforms are active, and collaborations with affiliated IMBB groups have formally commenced. Training activities have already started, including structured mentoring of postdoctoral fellows and PhD students, laboratory-based skills development, and participation in seminars and advanced methodological workshops. Grant preparation and network expansion efforts are underway, with new proposals in development. Administrative coordination mechanisms have been implemented, strengthening project management and integration with existing infrastructures. Together, these steps mark the transition of InflaCare from planning to full scientific and institutional executio**.**

Plant & Plant-Microbe Biology



Kriton Kalantidis

Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Senior research assistants: Konstantina Katsarou
Postdoctoral researchers: Nikoleta Kryovrysanaki
PhD students: Martha Tselika, Lena Michaelidou
MSc students: Sofia Roussaki, Christiana Spyridaki
Undergraduate thesis students: Maria Eleni Bitti, Tryfonas Chletsos

PLANT BIOLOGY & RNA BIOLOGY

Summary

Our main interests include viroids, non-coding cellular RNA parasites, and their interaction with their hosts. In addition, we are interested in the 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.

Current aims

1. Investigating key steps of the viroid biological cycle, such as replication and cell-to-cell movement.
2. Decipher mechanistic and evolutionary aspects of RNA silencing, primarily, but not exclusively, in plants.
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).

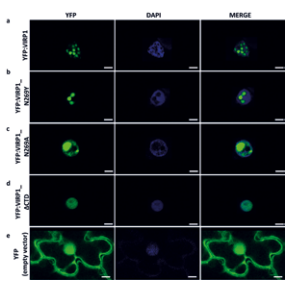
1. Viroids rely fully on host factors for the completion of their biological cycle; to understand viroid biology it is important to isolate and characterize the host-interacting factors.
2. Cellular RNAs (both large and small) as well as pathogenic RNAs use extracellular vesicles (EVs) to move from one cell to another. In plants, this process is much less studied, and our current work focuses on how these RNAs use EVs to move between cells and within the plant.
3. We furthered our understanding of the role of the 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. Using these tools, we defined the role of some RTL proteins in plant defense against RNA cellular parasites.
4. 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.
5. Having sequenced the first Carob genome, we re-sequence specific wild and cultivated genotypes. In addition, we are working on evolutionary and biochemical aspects of the Carob genome.

Progress in 2024-2025

1. We have shown that VIRP1 is a host factor substantially for viroid replication. We have shown that its its involved in ABA-related phenomena and also functions as a transcriptional regulator. We have now managed to purify VIRP1 and shown that this protein is able to form phase separation in vitro and in vivo. In addition, we have shown that VIPR1's bromodomain integrity is critical for its role in viroid infectivity.
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 developed an EV enrichment protocol for *Nicotiana benthamiana* and *Solanum lycopersicum* leaves which yields EVs of high quality and quantity. A proteomic profile of these EVs has already been completed, and we are currently working on their transcriptomic profiling, both in the absence and presence of various viruses and viroids.
4. We have generated RNAi mutants for 3 RTL proteins in *N. benthamiana* and with these lines we have revealed a role for at least two of these proteins in plants' defense against viroids.
5. In addition to the chromosome-level sequencing of the Carob genome and the re-sequencing of four more additional genotypes we have shown that genetically this *Fabaceae* species has lost the ability to do symbiotic interactions with rhizobia in order to take advantage of atmospheric nitrogen fixation.

Other Activities

- Booth at "Researchers Night" to interact with public via hands-on experiments with plants. (2024 and 2025)
- Keynote speech at 'Viroids, viroid-like RNAs and RNA viruses' meeting. (Bari 22-24 September 2025)
- Invited talk at the Hellenic Darwin Day organized by the Hellenic Evolutionary Society, Natural History Museum of Crete in Heraklion on February 17, 2024
- Ingenium Winter School 2024. "The Carob Challenge: A Paradigm of Sustainable Development and Innovation" Together with Cultural Society Epimenidis and UoC. February CarobMill, Panormo



Confocal microscopy showing localization of tomato VIRP1 and mutants/truncations. Intact tomato VIRP1 (602aa) forms distinct puncta in the nucleus (a); bromodomain mutations N269Y and N269A lead to bigger in size and less abundant nuclear puncta (b,c); truncation of VIRP1 CTD, forming the fragment 1-400aa, leads to a disperse distribution in the nucleus (d). Free YFP was used as a control (e). DAPI was used as a nuclear marker; scale bar=5μm.

Web page https://www.imbb.forth.gr/en/research/Kriton-Kalantidis.78/

Publications

Bardani E, et al. (2025) Broadening the Nicotiana benthamiana research toolbox through the generation of dicer-like mutants using CRISPR/Cas9 approaches. **Plant Sci.** 356:112490

Eldahshoury MK, et al. (2024) Isolation of Small Extracellular Vesicles (sEVs) from the Apoplastic Wash Fluid of *Nicotiana benthamiana* Leaves. **Curr Protoc.** 4(11): e70026

Grypioti E, et al. (2024) Dicer-dependent heterochromatic small RNAs in the model diatom species *Phaeodactylum tricornutum*. **New Phytol.** 241(2):811-826

Panagiotis N. Moschou

Associate Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Postdoctoral researchers: Michel Heidecker, Adrian Suarez Covarrubias, Jose Pepe Moya, Konstantin Kutashev, Ashwani Kumar Verma, Maity Shukendu
Technical Assistants: Maria Papadovasilaki, Athanasia Christopoulou, George Vlachakis, Maria Kalitsounaki (PhD)
PhD students: Fanourios Mountourakis, Fatemeh Barazandeh
MSc students: Michailidou Christina, Argyris Kolias, Zoumpoulia Vertoudou
Undergraduate thesis students: Eleni Manassaki, Konstantina Vavitsa, Chrysanthi Vasilaki

PLANT EPIGENETICS & MOLECULAR PHYSIOLOGY

Summary

The Plant Molecular Physiology Group focuses on the molecular mechanisms that govern (plant) growth, stress adaptation, and cellular organisation. Our mission is to understand how plants integrate environmental signals with internal developmental programs to maintain cellular homeostasis and optimise their physiology. We combine molecular biology, genetics, advanced imaging, and systems approaches to study:

- Cytoplasmic condensates and phase separation as regulators of plant stress adaptation
- RNA-protein interactions during developmental transitions and environmental cues
- Post-translational regulation (e.g., protein ubiquitination, phosphorylation, proteolysis) in membrane trafficking and cellular signaling
- Cell wall sensing and remodelling in response to hormonal and mechanoperception
- Spatiotemporal coordination of signalling pathways in root and shoot development

Our work bridges molecular physiology with emerging areas such as liquid-liquid phase separation, spatial transcriptomics, and organelle biophysics.

Current aims

Our group seeks to uncover how regulatory layers, ranging from signalling networks to RNA and protein dynamics, coordinate organismal responses and cross-organismal communication). Our vision is to address fundamental biological questions while contributing knowledge that can enable sustainable agricultural innovation (e.g., using crops). The group maintains a collaborative, interdisciplinary ethos, integrating cutting-edge tools such as: live-cell and super-resolution microscopy, genome editing (CRISPR/Cas) and genetics, proximity labeling (proximomes) and interactome mapping, transcriptome and proteome profiling under dynamic conditions, synthetic biology for pathway reconstruction, molecular dynamics and biophysics and *in vitro* reconstitutions. We use model systems such as *Arabidopsis thaliana* and *Nicotiana benthamiana*, while also exploring translational applications in crop species, such as tomato. By elucidating how plants organize molecular processes in time and space, our research contributes to:

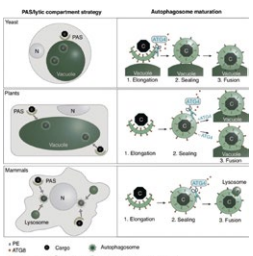
- Discovery research on biology
- Solution research for improving (plant) stress resilience and productivity
- Training the next generation of scientists mainly for academic setting
- Keeping up with requirements for internationalization and dissemination activities
- Teaching activities within this context

Progress in 2024-2025

We strategically expanded our research along three interlinked axes: mechanistic insight, technological innovation, and translational relevance. The group now manages to study processes within protein-RNA condensates in timescales of nanoseconds up to months and include dynamics at the single molecule all the way to organismal level. We aim to further focus on RNA-protein assemblies that are assembled through the help of membrane dynamics in cells, to leverage our recognized expertise in the field. We have introduced the relevant concepts into the literature through important and well-cited reviews and papers (Liu *et al.*, 2024, Maity & Moschou, 2025, Di Fino *et al.*, 2025). We suggest that condensates can form through non-canonical processes, by templating on specialized foci of membranes with certain geometric rules that resemble the so-called vertices (the idea supporting our ERC project PLANTEX; 10.3030/101126019). This body of work fundamentally changed how the field views plant stress responses, shifting from a model of linear signaling cascades to one of quasi 2.5 D. and 3D, phase-separated organizing centers atop membranes that orchestrate multi-level responses (e.g., autophagy; Fig. 1).
To accomplish these tasks, we integrated spatial omics approaches, including transcriptomics and proteomics, with high-resolution live-cell imaging to map cellular organisation *in planta* with unprecedented precision. For example, we built an expansion microscopy approach combined with high resolution in situ sequecing (the stereoseq approach). We further tested the interaction rules that build these condensates using advanced genetics to perturb specific sequences that we have obtained using machine learning approaches. The discovery of such "emergency" condensate assemblies and the new rules that we have discovered that underpin their formation in plants has broader implications. From a technological standpoint, we invested in developing and implementing synthetic biology tools to perturb and reconstruct key signaling modules in condensates, while extending the use of proximity labeling (to identify novel condensates and their dynamics), CRISPR-based reporters, and single-molecule imaging. Additionally, the group built a variable angle TIRFM that will allow deciphering 2.5 condensates in super-resolution, which has not been done before.
Strategically, we strengthen national and international collaborations, and achieved competitive funding, contributing to training through involvement in graduate programs and co-supervision networks. We further explored translational pathways by applying core discoveries to stress resilience traits in crops with a strong focus on tomato, supporting the Center's broader mission in sustainability and bio-innovation.

Other activities

- Competitive grants: EMBO Advanced Collaborative Grant and an HFRI Grant, among others.
- Teaching excellence: The PI is the director of the MS program "Green Biology" at the University of Crete.
- Decision making and policy: active role in the discussions about the usage and applications of CRISPR in plant biotechnology.
- Dissemination/internationalization: The PI organized an International Conference on Arabidopsis Research 2025 session on Condensates in Ghent, Belgium and gave >20 invited talks.



A recent discovery that the group contributed to, showing that in some plants autophagosomes do not require the protease ATG4 (Zou et al., 2025; DOI: 10.1038/s41467-024-55754-1).

Web page https://pmoschoulab.blog/home/

Publications

Di Fino L M, et al. (2025) Cellular damage triggers mechano-chemical control of cell wall dynamics and patterned cell divisions in plant healing**. Dev Cell** 60: 1411-1422 e1416
Liu C, et al. (2024) A proxitome-RNA-capture approach reveals that processing bodies repress coregulated hub genes. **Plant Cell** 36: 559-584.

Panagiotis F. Sarris

Associate Professor / Biology Department, University of Crete –Collaborating Faculty Member

GROUP MEMBERS

Senior postdoctoral researchers: Vassiliki Michalopoulou, Savvas Paragkamian
PhD students: Nikos Arapitsas, Maria Pires (MCSA student, Portuguese)
Visiting students: Alessandro Marchetti (PhD student, from Prof. Marianna Lotti's Lab, UNIMIB, Italy - 2024)

MICROBIOLOGY, MOLECULAR HOST–MICROBE INTERACTIONS & PLANT IMMUNOBIOLOGY

Summary

Our group is passionate about microbes — both beneficial and pathogenic — and the molecular strategies they employ to colonize their hosts. Using functional patho-genomics and patho-proteomics, we investigate:

- Microbial strategies for host colonization (e.g., effector proteins).
- Host innate immunity system 's function.

We primarily use plants as model organisms to study Molecular Host-Microbe Interactions (MHMI), with a focus on the fundamental "molecular dialogues" between host and microbe. Our interests extend to microbial and plant comparative genomics, metabolomics, transcriptomics and epigenetics.

Current aims

Understanding microbial colonization in plants and animals requires elucidating:

1. Host immunity mechanisms,
2. Microbial virulence strategies.

Key areas of focus:

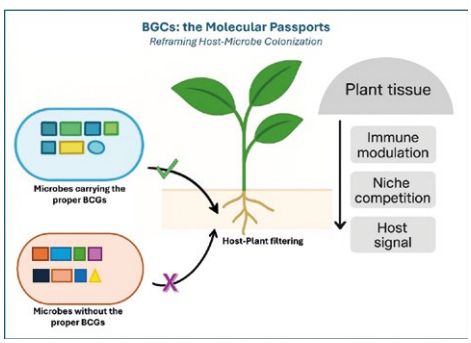
- Pathogens deliver virulence proteins ("effectors") into host cells. Determining their roles and targets is crucial for understanding host-pathogen interactions.
- Intracellular NLR immune receptors in plants and animals detect pathogens, often triggering programmed cell death (PCD). We discovered that certain plant NLRs contain additional integrated domains (IDs) that act as "decoys" for pathogen effectors. These IDs originated from duplications of effectors' virulence targets.
- Our group studies how plants resist disease via NLR-IDs and how pathogens overcome this resistance, with emphasis on effector targets and defense activation.

We also explore the cultivated microbiome of crop wild relatives (CWR) from extreme environments, investigating their potential as:

- Biopesticides,
- Biofertilizers,
- Sources of antimicrobial, anticancer, and anti-inflammatory compounds.

Progress in 2024-2025

- Secured funding from the **EU HORIZON-MSCA-2023 grant** and submitted multiple national grant applications.
- Published seven papers in high-impact journals, including *The Plant Cell*, *Nature Genetics*, *Plant Communications*, and *iScience*.
- Expanded our **Biobank of beneficial microbes**, fostering collaborations across IMBB, foreign institutions and with private institutions.
- Initiated *in-depth* studies of cave microbes from Greece's deepest cave and established a European research network.
- Identified novel microbial species producing secondary metabolites with anticancer and anti-inflammatory properties, prompting a grant application.
- Established a student exchange collaboration with Prof. Marianna Lotti's lab at Università degli Studi di Milano-Bicocca (UNIMIB) to study extremophilic enzymes.



Other activities

- Coordinated a €1M project on halophytic microbiomes and bioactive plant components for sustainable food production.
- Renewal of Honorary Professorship, University of Exeter (2024–2026).
- Supervised numerous undergraduate and postgraduate students at the University of Crete
- PhD student Nikos Arapitsas was awarded **Best PhD Thesis and Thesis Presentation** of 2024, University of Crete.

Web page https://sarrislab.gr/ https://www.imbb.forth.gr/en/research/member-Panagiotis-Sarris.80/&uid=80&tab=97

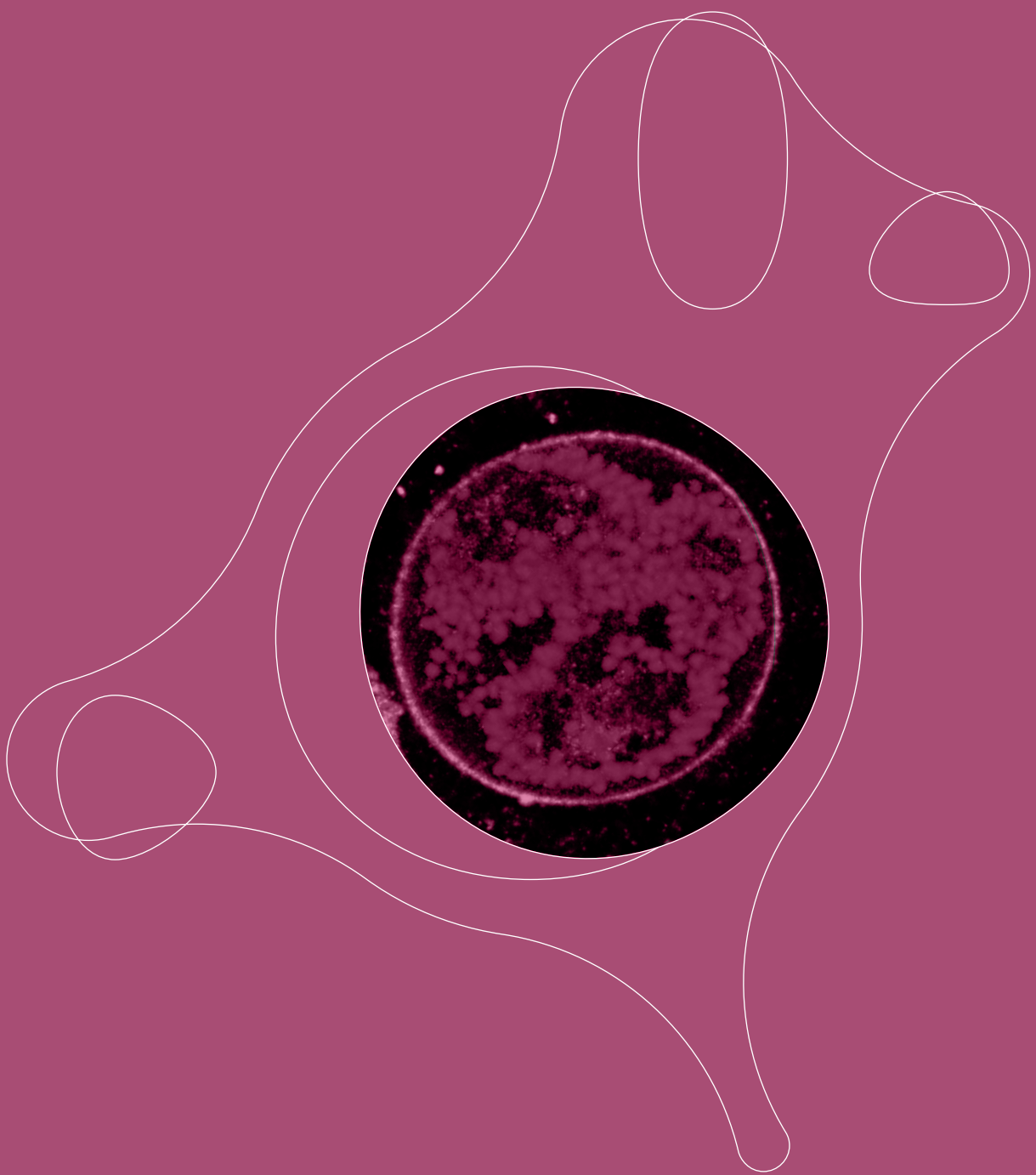
Publications

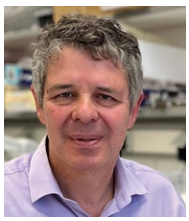
Chen R, et al. (2024) Genomic analyses reveal the stepwise domestication and genetic mechanism of curd biogenesis in cauliflower. **Nature Genetics** 56:1235–1244

Tsakiri D, et al. (2025) Subcellular targets and recognition mechanism of *Ralstonia solanacearum* effector RipE1. **iScience** 28:112307

Marchetti, et al. (2025). Xylan Degradation in the Halotolerant Bacterium Bacillus altitudinis relies on glycosidic hydrolases from families 11 and 30. **J Agric Food Chem. J.** 73:27599−27610

Insects and Vector Borne Diseases





John Vontas

Professor / Agricultural University of Athens –Collaborating Faculty Member

GROUP MEMBERS

Principal staff scientist: Linda Grigoraki
Postdoctoral researchers: Anastasia Kampouraki, Latifa Remadi, Kassiani Skouloudaki, Sofia Balaska, Rajeev Roy, Papapostolou Kelly, Rafaela Panteleri, Spyros Vlogianitis
Lab managers - technicians: Evangelia Morou, Dimitra Tsakireli, Giannis Pyrgiannakis
PhD students: Mengling Chen, Stefanos Mastis, Aikaterini Katsanou, Emmanouil Kokkas, Georgina Pantidi
MSc student: Chryssoula Nikolaou
Undergraduate thesis students: Ireni Kyvellou, Panagiotis Fouskarinis, Katerina Kladou

PEST AND VECTOR BIOLOGY & PEST CONTROL

Summary

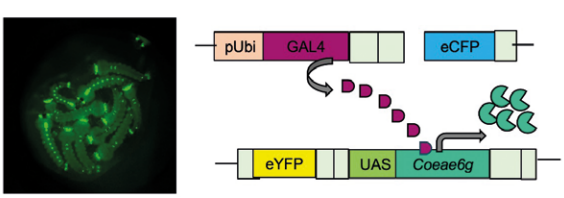
The Molecular Entomology group, led by Prof John Vontas, studies the mechanisms by which disease vectors and agricultural pests develop resistance to insecticides, as well as explores novel insecticide targets and biotechnology-based approaches to increase the efficiency and sustainability of insect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

Current aims

Insecticides are the cornerstones for controlling insects that are vectors of diseases or agricultural pests. However, the emergence of insecticide resistance, coupled with the limited availability of highly selective and environmentally safe compounds, presents a significant challenge for effective insect control. Our research focuses on elucidating the molecular mechanisms underlying insecticide resistance. We employ an integrated approach combining classical bioassays, omics technologies, and genetic and reverse-genetic tools to identify resistance-associated genes and mutations and validate their roles functionally. We also develop and apply molecular diagnostic tools to monitor resistance dynamics in field populations. In collaboration with academic and industry partners, we develop resistance breaking for incorporation into novel insecticide formulations. Additionally, our group uses state-of-the-art biotechnology-based approaches, including omics analyses and functional *in vivo* and cell-based assays, to characterize insecticide pharmacokinetics and identify novel insecticide targets in pest insects and mosquitoes. These targets are subsequently exploited for chemical library screening to discover compounds that induce mortality or reduce fertility, with an emphasis on high efficacy and species specificity.

Progress in 2024-2025

- The lab elucidated a carboxylesterase mediated resistance mechanism in the malaria transmitting mosquito, Anopheles gambiae. The Coeae6g esterase was found to underly resistance to Actellic300S (microencapsulated Pirimiphos methyl) a new and highly effective insecticide formulation, recently introduced in malaria control campaigns in Africa after many years of development (Balaska, Grigoraki et al Nat. Comms, 2025).



Transgenic *An. gambiae* pUbi- GAL4 > UAS- *Coeae6g mosquitoes*

- Significant progress was made in understanding the synergistic effect of resistance mechanisms in pests and malaria transmitting mosquitoes. A panel of transgenic mosquitoes carrying individual resistance mechanisms and their combinations was generated and used to validate their combined effect. Striking levels of resistance were observed in several combinations advancing our understanding of the mechanistic basis of insecticide resistance and having important implications for the design of accurate molecular diagnostics.
- Biopesticide solutions targeting major agricultural pests with high levels of insecticide resistance were developed, tested, and validated, with a focus on overcoming cytochrome P450 mediated detoxification mechanisms.
- We established efficient genome editing in lepidopteran species, allowing functional validation of genes involved in insecticide resistance and Bacillus thuringiensis (Bt) toxicity.
- Genomic resources in relation to insecticide resistance were generated for 11 Phlebotomine Sand Flies that will facilitate research on these important vectors of Leishmaniasis.
- The olive fruit fly is dependent upon a symbiotic bacterium for completion of the life cycle. Recently, we used advanced microscopy and omics methodologies to reveal the intricate relationships of host and symbiont in the adult stage. This project is in collaboration with Dr. Inga Siden Kiamos.

Other activities

- Coordinated: Next Generation Biopesticides (https://www.nextgenbiopest.eu/), Flagship action InnoPP (https://www.kainotomosfytoprostasia.gr/), Initiated a new project supported by the Gates foundation and participated in a number of EU consortia.
- Led the design and establishment of BSL2/3 facilities for work with transgenic organisms and experimental infections
- 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.
- ~ 10 undergraduate and master students received training and/or performed their thesis in the lab of Molecular Entomology
- Provided support and training to researchers from vector borne diseases endemic countries to advance their research in the field.

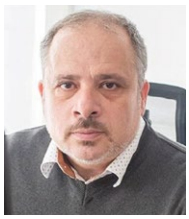
Web page https://www.vontaslab.gr/ https://www.imbb.forth.gr/en/research-en/biotechnology/item/2057-john-vontas

Publications

Balaska S, Grigoraki L*, et al. (2025) Predictive chemoproteomics and functional validation reveal Coeae6g-mediated insecticide cross-resistance in the malaria vector Anopheles gambiae. **Nat Commun** 16:10772 *co-corresponding author

Haba Y, et al. (2025) Ancient origin of an urban underground mosquito. **Science** 390(6771): eady4515

Charamis J, et al. (2024) Comparative Genomics Uncovers the Evolutionary Dynamics of Detoxification and Insecticide Target Genes Across 11 Phlebotomine Sand Flies. **Genome Biol Evol.** 16(9): evae186



Michail Kotsyfakis

Principal Researcher

Group establishment since April 2023

GROUP MEMBERS

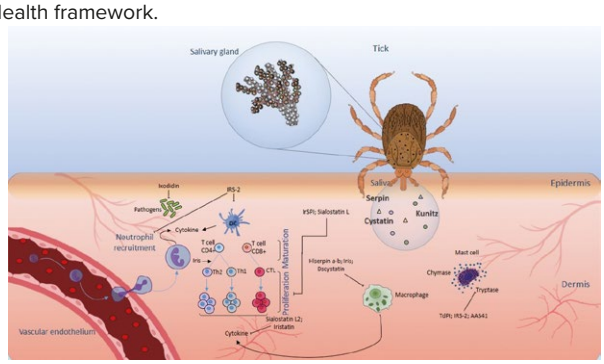
Postdoctoral researchers: Elena Deligianni, Zoi Veneti, Bartlomiej Ferra, Priyanka Upadhyay
PhD students: Konstantinos Kostas, Mequanint Addisu Belete, Noureddine Rabah Sidhoum
MSc student: Avery Hurst
Undergraduate thesis student: Foteini Ioanna Konsta

INSECTS & VECTOR BORNE DISEASES

Summary

The Tick Biology and Biotechnology group investigates ticks as model organisms to address fundamental and applied questions in disease vector biology, with emphasis on the molecular mechanisms that enable ticks to act as highly efficient disease vectors. Our research highlighted the central role of ticks at the interface of climate change, pathogen transmission, host immunity modulation, and biotechnology-driven innovation. A major objective is to strengthen tick surveillance and risk assessment, particularly in the Mediterranean basin, where climate-driven environmental changes increasingly favor tick expansion and pathogen emergence. In parallel, we investigate the molecular and biochemical basis of tick–host–pathogen interactions, focusing on salivary proteins, extracellular vesicles and their role in trans-kingdom communication, and regulatory RNAs that manipulate vertebrate host homeostatic responses against a feeding tick.

Beyond fundamental biology, our work has a strong translational orientation. We explore the biomedical and biotechnological potential of tick-derived molecules—such as protease inhibitors—as templates for drug development, biomarkers of tick exposure, and components of next-generation anti-tick vaccines. Collectively, these activities integrate basic discovery with applied research aimed at improving public health, animal health, and ecosystem resilience within a One Health framework.



Modern molecular approaches identify tick molecules that mediate tick vectorial capacity.

Current aims

1. Ticks, climate change, and disease risk
   Surveillance of tick populations and tick-borne pathogens, including emerging viral threats. Understanding how climate change alters tick ecology and geographic distribution. Development of preparedness strategies and integrated surveillance protocols.
2. Tick saliva biology and biotechnology
   Tick salivary composition and function: Comprehensive characterization of tick saliva using systems-level analyses to understand molecular mechanisms mediating ticktransmission lifecycle.
   Structure–function analysis of tick protease inhibitors: Investigation of the pluripotent pharmacological activities of tick salivary protease inhibitors, with validation in *in vivo* disease models.
   Anti-tick vaccines and exposure markers: Identification and validation of novel tick salivary antigens and biomarkers relevant to surveillance and control strategies.
   Regulatory nucleic acids in tick saliva: Study of tick-derivednon-coding RNAs, including their delivery via extracellular vesicles, and their role in modulating host gene expression.

Progress and Key achievements

- Functional-structural characterization of tick salivary cystatins, including Amblyostatin-1, Iristatin, and Ricistatin, revealing their relevance to host–pathogen interactions.
- Participation in the sequencing of four *Ixodes* genomes, providing new insights into tick evolution.
- Perspectives on climate change effects on Mediterranean tick populations and livestock systems.
- Advancement of translational pipelines that leverage tick-derived molecules as candidates for therapeutic development, diagnostics, and anti-tick vaccine research.

Some of the tick species found in Crete in dorsal and ventral views

Other activities

- Michail Kotsyfakis strengthened the *international visibility* of the group through leadership in collaborative consortia, invited lectures including a virtual one in the 80th United Nations General assembly Science Summit, and participation in global scientific networks.
- *Editorial duties*: Associate Editor, International Journal of Molecular Sciences; Frontiers in Cellular and Infection Microbiology; BMC Genomics; Life (Basel).
- Teaching: Graduate Program “Molecular Biology and Biomedicine” and “Immunobiology”, University of Crete.
- The group provided *structured research training* to PhD, MSc, and undergraduate students from Greece and abroad, supported by substantial external competitive funding. *Major international grants coordinated by the group*, include the EU HORIZON ResTick consortium (€6.13M total; €1.19M to IMBB–FORTH) and the Human Frontiers Science Program research grant (€1.5M total; €0.375M to IMBB–FORTH), ensuring exposure to state-of-the-art methodologies in tick ecology, molecular biology, protein expression, and functional analysis of tick salivary molecules. Three externally funded PhD projects address tick ecology, while MSc, Erasmus, and undergraduate trainees gained hands-on experience in translational biotechnology pipelines.

Web page https://www.imbb.forth.gr/en/research/Michail-Kotsyfakis.83/

Publications

Cerqueira de Araujo A, et al. (2025) Genome sequences of four Ixodes species expands understanding of tick evolution. **BMC Biol.** 23:17
Xiong W, et al. (2024) Cathelicidin-HG alleviates sepsis-induced platelet dysfunction by inhibiting GPVI-mediated platelet activation. **Research** 7:0381
Wu H, et al. (2024) Tick cysteine protease inhibitors suppress immune responses in mannan-induced psoriasis-like inflammation. **Front Immunol.** 15:1344878

Inga Siden-Kiamos

Emerita Principal Researcher

GROUP MEMBERS

Postdoctoral researchers: Chiara Currà (currently Researcher at Istituto Superiore di Sanita, Rome), Elena Deligianni
PhD student: Claude Preira
Special research assistants: Lefteris Spanos, Renate Gessmann

PARASITOLOGY

Summary

Two systems of microbes and insects: malaria parasite in the mosquito and bacterium-fly symbiosis in the olive fruit fly

The major research area of the group continues to focus on *Plasmodium*, the unicellular protozoan parasite that causes malaria. Malaria constitutes a serious threat to human health, especially in the poorest countries of the world, with more than half a million deaths reported each year. The parasite is transmitted by mosquitoes. Our laboratory investigates the basic biology of the parasite with emphasis on the mosquito stages, using reverse genetics and cell biology. The overall goal is to develop strategies to control the disease by blocking transmission through mosquito. The laboratory is also involved in a project aiming to elucidate the role of the symbiotic bacterium *Candidatus* Erwinia dacicola in the life cycle of the olive fruit fly *Bactrocera oleae* (in collaboration with Vontas group). This insect is a major pest of olives, and has a severe economic impact on olive production. The aim of this project is to develop methods to target the bacterium for control the fly.

Current aims

1. In the mosquito the parasite goes through a complex series of developments, that lead to the formation of the infectious sporozoite, which is the stage of the parasite that is transmitted to a new host when the mosquito takes a second blood meal. The sporozoites develop in the so-called oocyst, a stage of the parasite dedicated to the proliferation of the parasite. This stage is not well understood and our aim is to characterize the oocyst and especially the cyst wall, a protective capsule surrounding the cell. The knowledge obtained can be used to identify inhibitors that interfere with the oocyst and thus block transmission of the parasite.
2. Actin dynamics in the malaria parasite is divergent from that of higher eukaryotes. Specifically, a limited number of actin binding proteins regulating actin polymerization are present in the parasite and their functions are unusual. We have focused on the actin-binding protein C-CAP, which has an essential function in the development of the oocyst, with the goal to understand when and where the protein is required.
3. Our study of the olive fruit fly *B. oleae* and its symbiotic bacterium *Ca.* E. dacicola aims to deepen our understanding the symbiotic relationship and explore whether targeting this interaction can be a strategy to control the fly.

Progress in 2024-2025

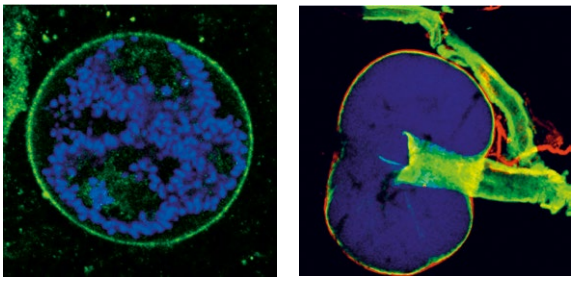
The rupture of the wall of the oocyst and concomitant release of the infectious sporozoites depends on the Oocyst Rupture Proteins (ORPs). Previously, we have characterized two of these, and we have now identified and characterized a third protein, ORP3. These three proteins have similarities to the NF-Y DNA binding factor of higher eukaryotes, but in the parasite their function is restricted to oocyst rupture, and they are all present in the oocyst wall. Similar to NF-Y they form a trimeric complex and we have identified peptides that interfere with complex formation; these are starting points for development of inhibitors blocking transmission through the mosquito.

To understand the function of C-CAP we determined the expression of this protein using western blot and immunofluorescence. While the lack of C-CAP leads to abnormal oocyst development we found that the protein is only expressed in the earlier stages (gametes, zygote, ookinete). We generated a mutant expressing C-CAP fused to an auxin inducible degron domain with the aim to understand at which stage the protein is required. However, this mutant unexpectedly acted as a dominant negative, as the mutant was not transmitted to naïve mice despite the fact that development in the mosquito was normal. This suggest that C-CAP has a hitherto unknown function in the early liver stages in the mammal.

Our investigation of the interaction of the symbiont *Ca.* E. dacicola with the adult olive fruit fly has focused on the three organs which harbor the bacterium, the esophageal bulb (EB), midgut and ovipositor. We have used a combination of proteomics and advanced imaging and this has revealed that the bacterium has a different metabolic profile in each of the three organs, with DNA replication only happening in the EB, while in the ovipositor the symbiont is metabolically inactive. Importantly, in the EB *Ca.* E. dacicola expresses enzymes involved in nitrogen uptake while the EB itself mainly acts in transport. This finding explains the need for the symbiont for nutrition of the adult fly which feeds on nitrogen poor diets. We are also investigating whether the bacterium forms biofilm to protect itself from the insect.

Other activities

- Our laboratory participated 2024 in the European outreach activity Researcher's Night (funded by Marie Sklodowska Curie action) presenting our work on mosquitoes and malaria to the general public.
- The PI is a member of EU-Life Communications working group as well as member of the Science Communication team at IMBB.



Left: oocyst of the malaria parasite expressing ORP3 (green, DNA, blue). Right: the esophageal bulb of *B. oleae* (red, green) with bacteria in the lumen (blue)

Web page https://www.imbb.forth.gr/en/research/Inga-Siden-Kiamos.85/&tid=85

Publications

Preira C, et al. (2024) A time point proteomic analysis reveals protein dynamics of Plasmodium oocysts. **Mol Cell Proteomics** 23(3):100736

Siden-Kiamos I, et al. (2025) The Journey of the Bacterial Symbiont Through the Olive Fruit Fly: Lessons Learned and Open Questions. **Insects** 16: 789. Review

Linda Grigoraki

Principal Staff Scientist-
Vondas lab

PEST AND VECTOR BIOLOGY & PEST CONTROL

Vector-borne diseases cause morbidity and mortality in many developing countries, with malaria alone being responsible for close to 600,000 deaths in 2023. Resistance to insecticides in *Anopheles gambiae*, the primary malaria vector in sub-Saharan Africa, is a primary factor underlying the stagnation of efforts to eliminate malaria. I use functional genetics to understand the molecular basis of insecticide resistance in vectors of diseases and reveal the relative contribution of genes and mutations in the resistance phenotype (Balaska, Grigoraki* et al Nat. Comms, 2025). The past two years we have worked on elucidating how high levels of resistance arise and have highlighted the synergistic action of different mechanisms. I have also expanded research on volatile pyrethroid insecticides, that have received WHO pre-qualification for malaria control. We have shown in collaboration with researches from the Liverpool School of Tropical Medicine and the Benaki Phytopathological Institute the high risk of cross resistance to contact pyrethroids, providing essential information to support evidence based decisions for their deployment in vector borne diseases control. In 2025 I became an associate editor at the Pest Management Science Journal.

Teaching at the Plant Molecular and Applied Biology - Green Biotechnology master program of the Biology Department, University of Crete.

Pantelis Topalis

Senior Staff Scientist

GENOMICS & DATABASES

My main interests are

a) to analyze gene expression and regulation from high throughput sequencing datasets,
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, we assisted with the discovery of plant viruses and viroids in *Ceratonia siliqua* genome based on RNA-seq data and we will be focusing on developing tools to facilitate the subtyping of *Olea europaea* in Greece based on morphological and molecular analyses.

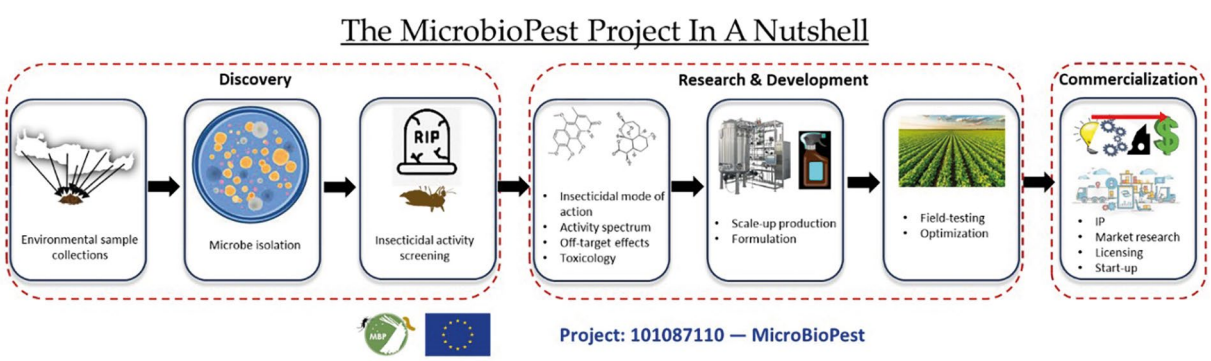
George Dimopoulos

Johns Hopkins Malaria Research Institute

Adjunct Researcher, ERA Chair IMBB-FORTH

VECTOR BIOLOGY-BIOTECHNOLOGY

In 2022, Prof. George Dimopoulos (Johns Hopkins University & IMBB alumnus) joined IMBB as its inaugural ERA Chair to strenghten the Vector Biology/Green Biotechnology division. His research investigates the complex interactions between mosquitoes and pathogens to develop innovative disease intervention strategies. Currently, his program focuses on harnessing the innate immune systems and microbiomes of *Anopheles* and *Aedes* mosquitoes to block the transmission of malaria and arboviruses. Additionally, Prof. Dimopoulos leads the MicroBioPest team, a translational research initiative dedicated to developing eco-friendly, cost-effective microbial biopesticides. By utilizing state-of-the-art methodologies to identify insecticidal microorganisms and their modes of action, the team aims to create sustainable prototype niopesticides for controlling both disease vectors and agricultural pests. An international team was established at IMBB in 2022 comprising 3 postdoctoral fellows, 2 PhD graduate students, and master and undergraduate trainees, along with an administrative analyst. Disparate habitats in Crete were surveyed extensively to establish a library of about 1700 bacterial and fungal isolates of which the majority were screened for larvicidal activity against *Culex pipiens*. Results demonstrate promising potential of several of bacterial and fungal isolates, with over 40 unique isolates exhibiting potential for the development biopesticides. Spectrum or activity, biochemical, molecular and genomic analyses have narrowed in on 6 isolates that are pursued for prototype product development. The mode of action of these isolates involves both protein- and metabolite-mediated insect-killing. Ongoing work is focusing on the characterization of their active ingredients (the molecules mediating insect killing), their mechanistic mode of action, off-target effects, development of formulations and semi-field testing.



Publications

Wood MJ, et al. (2025) Bacteria isolated from biodiverse Mediterranean island habitats yield a large array of biopesticidal metabolites against mosquito larvae. **Appl Environ Microbiol.** 91(8):e0096625

Affiliated and Adjunct Faculty

Alex Dömling

University of Groningen

CHEMICAL BIOLOGY

George Diallinas

Universiy of Athens

REGULATION OF CELLULAR EXPRESSION, STRUCTURE, FUNCTION AND EVOLUTION OF TRANSPORTERS

Jean-Paul Latgé

Institute Pasteur

INFECTIONS AND IMMUNITY

Triantafylos Chavakis

Technical Univ. Dresden

INNATE IMMUNITY AND IMMUNOMETABOLISM

Michail Lionakis

NIAID/NIH

CLINICAL IMMUNOLOGY AND MICROBIOLOGY

Ioannis Mitroulis

Technical Univ. Dresden

INNATE IMMUNITY AND HEMATOPOIESIS

Paul Lasko

McGill University

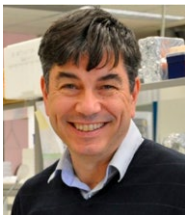
TRANSLATIONAL GENE REGULATION

Nicholas Katsanis

Galatea Bio and Antithesis Therapeutics

GENETICS, CELL BIOLOGY & DRUG DISCOVERY

Facilities



Iannis Talianidis

Scientific Director, Head of Facility

Theodoros Kosteas

Co-Head of Core Facility

FACILITY MEMBERS

Veterinarians: Costas Kourouniotis, Eleni Moltsanidou, Debbie Tsoukatou (part time)
Special Research Assistant: Eva Livadara
Animal Technologist: Hara Roumpaki, Irene Voskaki
Animal Technicians: Eleni Ntagiasi, Androniki Vardoulaki, Stella Chalkiadaki, Konstantina Sarri, Eirini Charitaki
Support Technician: Ektoras Xenakis

ANIMAL (MOUSE)/ GENOME EDITING CORE 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 25 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 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 2024-2025

- Eva and Irene join our team.
- Received Animal Welfare Assurance from the NIH Office of Laboratory Animal Welfare (OLAW).
- Purchased a new IVC unit and the Mausoleum colony management software.

Selected impact activities

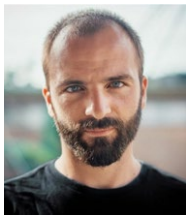
Members from our facility participated in various meetings, committees and courses:

- Annual 10th and 11th FELASA accredited Course on the Care & Use of Laboratory Animals.
- National committee for the protection of animals used for scientific purposes.
- EU-LIFE Core Facilities Working Group & Community meeting.

i) Genome Editing Lab ii) Cage/bottle washer iii) Air shower unit

Web pages

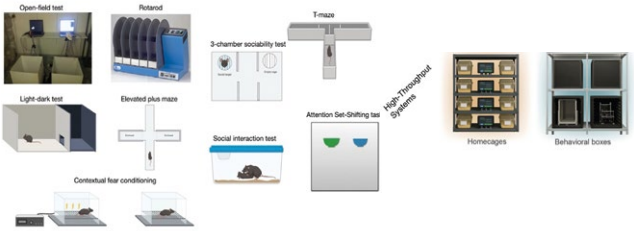
https://www.imbb.forth.gr/imbb-people/en/animal-house
https://www.infrafrontier.gr/phenotypos
http://www.felasa.eu/working-groups/guidelines/felasa-guidelines-and-recommendations/
https://eu-life.eu/research-excellence/working-groups-task-forces/core-facilities



Emmanouil Froudarakis

Head of Unit

BEHAVIORAL UNIT



Summary

The Behavioral Unit, led by Dr. Emmanouil Froudarakis and Dr. Kyriaki Sidiropoulou, is a core research infrastructure facility within the IMBB Animal House, with an additional satellite facility located at the main Institute premises. The Unit supports systematic and quantitative assessment of rodent behavior, providing essential infrastructure and expertise to enable high-quality, reproducible investigations in accordance with international standards. It plays a central role in facilitating research at the intersection of neuroscience, physiology, and molecular biology, supporting experimental workflows from design to analysis and interpretation.

Capabilities

The Behavioral Unit offers a comprehensive suite of experimental and analytical capabilities for behavioural neuroscience research, including:

- **Behavioral testing infrastructure:** Fully equipped arenas and devices for a wide array of behavioral paradigms, enabling quantitative assessment of locomotion, motor coordination, anxiety-related behavior, memory and object recognition, social behavior, sensory discrimination, and multisensory integration.
- **Advanced tracking and measurement systems:** High-resolution video tracking and sensor integration provide unbiased and precise quantification of animal behavior with automated data acquisition.
- **Experimental design support:** Consultation and assistance with task selection, protocol optimization, and experimental setup to enhance rigor and reproducibility.
- **Data analysis pipelines:** Dedicated software platforms and analysis workflows that support large datasets and ensure consistent, reproducible processing of behavioral metrics across studies.
- **User training and support:** Technical training for researchers in both hardware use and analytical tools, fostering best practices and ensuring high-quality experimental outcomes.

Progress in 2024-2025

The Behavioral Unit enhanced its automation and data standardization capabilities through the adoption of **EthoPy**, an open-source Python-based platform for behavioral control and training. EthoPy supports modular experimental design, automated stimulus presentation, real-time data acquisition, and comprehensive metadata recording, thereby promoting reproducible and scalable behavioral workflows. Its implementation in selected experimental paradigms has strengthened the Unit's capacity for automated training, high-throughput data collection, and standardized analysis procedures, further reinforcing methodological rigor and reproducibility across supported research projects.

Web page https://www.imbb.forth.gr/en/facilities/Behavioral-Unit.9/

Publications Evangelou A*, Diamantaki, M*, et al. (2025). EthoPy: Reproducible Behavioral Neuroscience Made Simple. **bioRxiv** doi:10.1101/2025.09.08.673974

Stavroulaki V*, Vagiaki* L-E, et al. (2025) Effects of working memory training on cognitive flexibility, dendritic spine density and long-term potentiation in female mice. **Behav. Brain Res.** 115555 doi:10.1016/j.bbr.2025.115555

Kokkali M, et al. (2025) Multimodal beneficial effects of BNN27, a nerve growth factor synthetic mimetic, in the 5xFAD mouse model of Alzheimer's disease**. Mol Psychiatry** 30:2265-2283

Kyriaki Sidiropoulou

Head of Unit

ELECTROPHYSIOLOGY UNIT

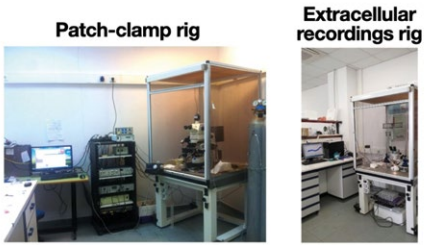
Description

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

Progress in 2024-2025

During 2004 and 2025, we have performed several experiments testing the effects of novel drugs on spontaneous neuronal activity and synaptic plasticity. We have also studied the synaptic properties and intrinsic properties of pyramidal neurons and specific types of interneurons across development and in an animal model of schizophrenia.



(left side) The system set-up used to perfrom current-clamp or voltage-clamp recordings from brain slices and/or cell cultures. **(right side)** The system set-up used to performed spontaneous activity and synaptic plasticity experiments using extracellular recordings from brain slices.

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

Publications Vagiaki L-E, et al. (2025) Region-specific modulation and predictive potential of the oscillatory dynamics, **Neuroscience letters** 866:138367

Stavroulaki* V, Vagiaki* L-E et al. (2025) Effects of working memory training on cognitive flexibility, dendritic spine density and longterm potentiation in female mice, **Behav. Brain Res.** 115555

Spanaki* C, Sidiropoulou* K, et al. (2024) Glutamate-specific Gene Linked to Human Brain Evolution Enhances Synaptic Plasticity and Cognitive Processes. **iScience** 27(2):108821. eCollection 2024 Feb 16. *equal first author

Christos Andronis

Bioinformatics Lead

FACILITY MEMBERS

Senior Staff Scientist:
Pantelis Topalis

Facility Member:
George Papagiannakis

Data Management & Analysis:
Manolis Dialynas

Special Research Assistant:
Electra Tsaglioti

BIOINFORMATICS UNIT

Summary

High-throughput sequencing technologies are increasingly becoming a fundamental part of modern biological research. At IMBB, the Bioinformatics Unit serves as a core hub that connects experimental groups with computational expertise in bioinformatics, leveraging sound, reproducible methodologies, appropriate quality control, and scalable infrastructure to enhance the Institute's research output.

Services and Capabilities

The Bioinformatics Unit currently provides support for differential gene expression analysis, transcriptome assembly and annotation, variant analysis (including SNPs and indels), ATACseq, ChIPseq, and epigenomic analyses, phylogenetic analyses and comparative genomics, pathway and gene set enrichment analysis, custom workflow and pipeline automation, and data visualization and reporting. The Unit's expertise spans experimental technologies and analytical approaches, enabling researchers to address complex biological questions across diverse organisms. In addition to its core bioinformatics data analysis services, the Unit is involved in developing web applications customized to IMBB's research needs, maintains a computing infrastructure through a High-Performance Computing (HPC) cluster and several workstations, and promotes FAIR (Findable, Accessible, Interoperable, and Reusable) data and metadata principles to ensure research reproducibility and data accessibility. Experienced members of the Unit also provide training and mentoring on bioinformatics methods to lab members.

High Performance Computing Infrastructure

The Unit maintains a High-Performance Computing cluster in collaboration with the Genomics Facility, dedicated to computationally demanding bioinformatics analyses. The infrastructure provides researchers with access to multi-core processors, large memory capacity, and storage systems optimized for large-scale genomic data processing. The HPC computational environment supports standard bioinformatics software, custom analytical pipelines, and collaborative computing platforms for interactive data analysis. This infrastructure enables the processing of omics datasets and supports both routine analyses and computationally demanding research applications.

Progress in 2024-2025

In 2024, the Bioinformatics Unit at IMBB was officially established as a dedicated facility.

- This first year involved core work to establish the Unit's operational framework and service delivery capabilities. An initial priority was given to building a team of experienced bioinformaticians with broad expertise spanning genomics, transcriptomics, epigenomics, and computational biology. The team was assembled to provide a broad coverage of the analytical needs across IMBB research groups, with specialists in various omics technologies and analytical approaches.
- Significant effort was invested in constructing a robust project management infrastructure to ensure efficient workflow coordination and communication with researchers and users. This included implementing a web-based project-tracking system and a knowledge management wiki, creating a public website to raise visibility, and developing standardized procedures for project submission and follow-up. These organizational foundations enable the Unit to handle multiple projects while sustaining high standards of quality and reproducibility.
- An essential part of the first year's milestones was the recruitment of dedicated IT support to maintain and expand the High Performance Computing cluster. This investment provides reliable computing resources for the growing demands of omics analyses and positions the Unit to scale its infrastructure in response to evolving research needs. The computing infrastructure has been progressively consolidated and expanded, with continuous initiatives to augment storage capacity, processing power, and specialized capabilities, including GPU resources for machine learning applications.
- In its first year, the Unit handled over 30 bioinformatics projects covering a wide range of scientific topics and technologies. These projects included bulk RNAseq, ATACseq, transcriptome assembly, phylogenetic studies, and small RNA sequencing. This extensive work involved collaborations with researchers from multiple IMBB divisions and the University of Crete Medical School, establishing the Unit as a valuable resource for the Institute's research initiatives.

The Bioinformatics Unit collaborates closely with the IMBB Computing and Networks Group to maintain a strong computing infrastructure and partners with the IMBB Genomics Facility to provide seamless support from data generation to analysis. Through this integrated approach, the Unit advances IMBB's research mission by offering expert guidance, tools, and resources that enable cutting-edge biological discoveries. Moving forward, the Unit plans to expand its data analysis capabilities (e.g., in single-cell RNAseq), enhance its custom software development, and continue building infrastructure to support emerging technologies in multiomics, spatial transcriptomics, and integrative data analysis.

Web page	https://www.imbb.forth.gr/en/facilities/Bioinformatics-Unit.15/
Publications	All work performed by the Bioinformatics Unit should be acknowledged in presentations, reports, and all other publications.

Androniki Kretsovali

Head of facility

George Vrentzos

Head of facility

CELL CULTURE FACILITY

Summary

Since 1985, the Institute of Molecular Biology and Biotechnology (IMBB) has operated a fully equipped, self-contained Cell Culture Facility that supports the growth, maintenance, and analysis of animal cells. The facility provides essential services to investigators, including the preparation, filtration, and quality testing of a wide range of cell culture media, as well as access to sterile reagents and consumables.

Technical support is offered for:

1. The culture of diverse cell types, including mammalian and insect cell lines, hybridomas, and primary cells
2. Large-scale cell culture applications
3. Cell transfection and clonal expansion

The main facility is located on the first floor (Room A208) of the IMBB building and consists of three independent rooms equipped with HEPA-filtered airflow systems and UV sterilization. A second facility, located in the institute basement, supports insect cell culture, parasite transgenesis, and tissue engineering activities. All operations fully comply with European Union regulations for the handling and disposal of biohazardous materials.

Equipment

The Cell Culture Facility is equipped with:

- Ten biosafety level II laminar flow hoods for sterile cell handling
- Ten CO_2 incubators (37 °C) for mammalian cell culture
- Five incubators (25 °C) for insect cell lines
- Four refrigerated centrifuges

Progress and impact in 2024 and 2025

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.

Kriton Kalantidis

Head Of Facility

GREENHOUSE-CONTROL ENVIRONMENT ROOMS UNIT

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 540m^2 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. Cultivation takes place on elevated benches. All chambers are equipped with thermal curtains. Two chambers of a total 120m^2 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 years of report a large number of experiments have run in the glasshouse with a wide range of model and non-model plants including Arabidopsis, tobacco, tomato, cucumber, rice, beans, grapewine, avocado and citrus trees. 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.

Web page https://www.imbb.forth.gr/en/facilities/Greenhouse---Control-Environment-Rooms-unit.14/

Christos Delidakis

Head of facility

FACILITY MEMBERS

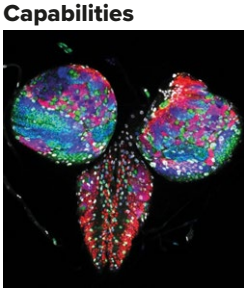
Postdoctoral researcher: Margarita Stapountzi
Lab Technician: Alexandros Babaratsas

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. It 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 near UV-visible – far red spectrum. The microscope is connected to an environmental chamber with controllable temperature and CO_2 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 2025 we had more than 100 accredited users from 38 research groups. If slots are available, we train and assist scientists from other FORTH institutes and nearby institutions (University of Crete) for their imaging needs.

A large variety of fixed and live samples are imaged in our facility, including cells (cell culture, animal/patient samples, cells on polymer scaffolds), dissected tissues (fruit flies, insects, crustaceans, mice, plants) or whole organisms (fruit fly embryos, nematode worms).

Progress in 2024-2025

No major changes took place, other than regular maintenance and repairs of the confocal unit, which has now reached 12 years since its installation, but is still in good functioning order.

Other activities

- Examples of recent activities supported by the facility are:
- Studying the cellular response to DNA damage
- 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 and fixed imaging of *Drosophila* neural tumours and their ability to differentiate
- Imaging of *Drosophila* intestine regeneration
- Live cell imaging of *Arabidopsis* root epidermal meristematic cells
- Studying nuclear lamin dynamics
- Imaging chromosomal territories by Chromosome Painting
- Imaging of cells cultured on 3D-printed scaffolds

Web page https://www.imbb.forth.gr/en/facilities/Confocal-Microscopy.10/

Publications The confocal Facility is acknowledged in a large number of the Institute's publications; below is a partial listing:

Veneti Z, et al. (2024) Polycomb-mediated silencing of miR-8 is required for maintenance of intestinal stemness in Drosophila melanogaster. **Nat Commun.** 15(1):1924

Kokkali M, et al. (2025) Multimodal beneficial effects of BNN27, a nerve growth factor synthetic mimetic, in the 5xFAD mouse model of Alzheimer's disease. **Mol Psychiatry** 30(6):2265-2283

Kalogeridi M, et al. (2025) Lineage tracing by light-sheet microscopy and computational reconstruction. **Methods Mol Biol** 2886:153-176

Mylonakis M, et al. (2024) Bimodal optical and optoacoustic multiview microscope in the frequency-domain. **Optics Letters** 49:462-465

Elena Deligianni

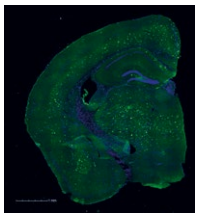
Head of the Unit

HIGH CONTENT SCREENING MICROSCOPY UNIT

The High Content Screening Microscopy (HCSM) facility provides services, including image acquisition, high-content analysis, and assay development for research groups within IMBB/FORTH and affiliated collaborators. In addition to routine high-throughput imaging, this year the facility expanded its capabilities by developing new analysis pipelines for whole-tissue visualization, segmentation, and quantification of protein expression in complex tissue samples. Complementary open-license software tools were incorporated to extend and enhance Harmony-based analyses when required. Live-cell imaging and long-term timelapse acquisition were further optimized, enabling dynamic monitoring of cellular processes in 2D and 3D systems.
The facility remains a central resource for high-content drug screening, phenotypic profiling, and quantitative cellular analysis, supporting a broad range of applications including cell growth and differentiation, apoptosis, autophagy, DNA damage, metabolic activity, Ca^{2+} signaling, and cell tracking. Ongoing development efforts aim to further expand 3D imaging workflows and integrate AI-assisted phenotype classification in the upcoming period.

Progress in 2024-2025

Facility usage was increased, supporting six new research projects during this period. Data generated through HCSM contributed directly to several high-impact publications, including:
Spanou et al. (2025) PML is crucial for neural stem cell differentiation, stress tolerance and mitochondrial integrity. **Stem Cell Reports** 20(9):102598
Galanopoulou O, et al. (2024) Endonucleosis mediates internalization of cytoplasm into the nucleus. **Nat Commun.** 15(1):5843
as well as two additional manuscripts currently under review.



Brain section from a 6-month-old mouse showing amyloid plaques labeled with GFP. Spanou et al., submitted.

Web page
https://www.imbb.forth.gr/en/facilities/High-Content-Screening-Microscopy-Unit.11/

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: Drosophila, medfly, olivefly, fall armyworm 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 six walk-in incubators with controlled humidity, temperature and light-dark cycle which surround the central Fly-room space. One is used exclusively for lepidoptera and two isolated spaces are dedicated to mosquitoes' rearing and handling.
- The central Fly-room space is a large lab with 4 work stations equipped with stereo-microscopes and anesthetization stages connected with a centralized CO_2-delivery system. A dark chamber with two stations for fluorescence stereo-microscopy completes the setup.
- Highly experienced technicians are responsible for the maintenance of insect stocks and provide technical assistance to researchers.
- 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). Additional microinjection equipment exists for transplanting tissues and inoculating pathogens into insect hosts.

Progress in 2024-2025

Two new stereoscopes were purchased to replace old overused equipment. The centralized CO_2 supply was upgraded.
Projects that have made extensive use of the facility:

- A pipeline for generating brain cell tumours in *Drosophila* was improved and extensively used for imaging and genomics studies.
- Development of biotechnology –based innovative approaches for mosquito and lepidoptera control.

Other activities

- The facility hosted visits and tours from high school students as part of school programs to promote careers in science.
- Hosting scientists from Africa and other parts of the world to be trained on functional genetics in insects and perform part of their research projects requiring established genome editing procedures and equipment.

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

Publications

Veneti Z, et al. (2024) Polycomb-mediated silencing of miR-8 is required for maintenance of intestinal stemness in Drosophila melanogaster. **Nat Commun.** 15(1):1924

Monastirioti M, et al. (2024) Notch-Dependent Expression of the Drosophila Hey Gene Is Supported by a Pair of Enhancers with Overlapping Activities. **Genes** 15(8):1071

Preira, C. et al. (2024) A time point proteomic analysis reveals protein dynamics of Plasmodium oocysts. **Mol Cell Proteomics** 23(3):100736

Camarero-Hoyos, C et al. (2024) Leveraging the Aggregated Protein Dye YAT2150 for Malaria Chemotherapy. **Pharmaceutics** 16(10):1290

Kefi M, et al. (2024) Insights into unique features of Drosophila CYP4G enzymes. **Insect Biochem Mol Biol** 164 :104041

Balaska S, et al. (2025) Predictive chemoproteomics and functional validation reveal Coeae6g-mediated insecticide cross-resistance in the malaria vector Anopheles gambiae. **Nat Commun** 16(1):10772

Zaharenia Vlata

Special Research Assistant, Head of Facility

Takis Makatounakis

Special Research Assistant, Head of Facility

FACS & 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 4 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 Institute of 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 four lasers: 1) **Violet - 405nm**, 2) **Blue - 488nm, 3) Yellow Green - 561nm** and 4) **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:

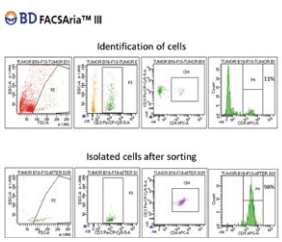
1. **488 nm Ion Laser Blue**-Green Argon,
2. **633 nm Red** Helium Neon laser.

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).

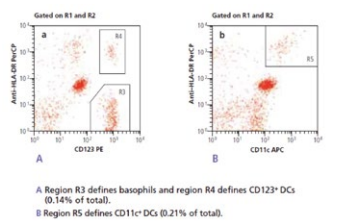
Progress in 2024-2025

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 5 of the University Hospital of Heraklion.

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



BD FACS Aria III Cell Sorter



FACSCalibur

Web page https://www.imbb.forth.gr/en/facilities/FACS-and-Sorting-Facility.4/

Marina Koukaki

Head of Unit

HISTOLOGY UNIT

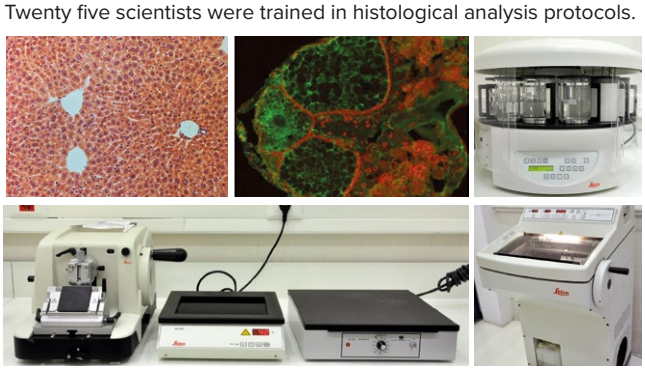
The Histology Lab is a Support Unit of IMBB equipped with Automatic Tissue Processor (Leica TP1020; Paraffin Embedding Station (Leica EG1150H)-Cold Plate (Leica EG1150C); Rotary Microtome (Leica RM2125) and (RM2255) - Water bath for Paraffin Sections (Leica HI1210) - Flattening Table for Clinical Histopathology; 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 2024-2025

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.



Web page https://www.imbb.forth.gr/en/facilities/Histology-Unit.6/

Matthieu Lavigne

Head of facility

FACILITY MEMBERS

Research assistant:
Eirini Stratidaki

Research assistant:
Niki Gounalaki

GENOMICS FACILITY

Summary

Next Generation Sequencing (NGS) technologies have been revolutionizing genetic, (epi)genomic and transcriptomic research, providing depth and details to understand mechanisms of transcription regulation, RNA processing or chromatin functions in healthy organisms as well as the impact of mutations in diseases. Numerous applications are routinely used in biomedical research and the IMBB Genomics Facility (GF) offers solutions as services for experimental consulting, quality control of samples, library preparation, sequencing to IMBB researchers and also external users (i.e. UoC, HCMR, NKUA, BRFAA). We assist scientists to advance their research by generating high quality and reproducible workflows that maximize the quality of sequencing data from difficult/precious samples. By optimizing techniques and by working close with the facility users, we offer a personalized experimental design, we discuss the best suited experimental approach, tailored to the projects needs and considering available resources. In other words, GF personnel provide robust technical advice on experimental plans/setups to enable better chances of project success. This helps researchers finding the best way to obtain high quality data and reliable results with best prices and rapid turnover time. A key aspect is that our service offers basic bioinformatics analysis and data interpretation without charge to guarantee access to the technology and maximization of the biological insights even to non-experienced users. As from 2025 GF head and IMBB researchers have created a *new Bioinformatics unit* that is dedicated to assist users of the facility as well as our institute's research community. We perform basic analyses as well as more advanced pipelines if needed including differential expression, transcriptome assembly and annotation, variant discovery (SNPs/indels), phylogenetics, pathway and gene set enrichment. We operate in project-centric and Researcher-friendly manner, providing assistance for users, even if sequencing service is not performed in-house (https://www.imbb.forth.gr/en/facilities/Bioinformatics-Unit.15/&tabid=Services.154.) During the last 2 years, the unit has improved and reduced the price for previously listed services such as bulk RNA-seq (3' quant-seq) and has worked to upgrade with state-of-the-art protocols services that include single-cell RNA-seq, bulk SLAM-seq and popular epigenomics assays (Cut-and-Tag, ChIP-seq, ATAC-seq, methylome-seq) services.

Capabilities

The facility has used the Illumina NextSeq 500 instrument historically and we upgraded our throughput and lowered our prices thanks to the acquirement of a Nextseq2000 in 2025. We also have access to a 10x Genomics chromium X, a LUNA FL for cell viability assays and a vortex for Fluent PIP-seq library preparation. Sequencing for specialized applications such as metagenomics is performed on Illumina MiSeq at HCMR, Heraklion.

The GF has several years' experience in the following services:

1. *RNA-sequencing (3', full-length, small RNA)*
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 Bioanalyzer, Thermo Scientific Qubit platform, qPCR...)

Progress in 2024-2025

The use of the facility has been extended with >1000 samples submitted in 2024-2025, assisting the research efforts of more than 25 IMBB, UoC and outside of Crete groups. 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 (only library prep kits, QC, flow cells and consumables are charged).

Highlights

- *Awarded a highly competitive Twinning HORIZON grant (SCENTINEL, 2024-27), a joint effort with 2 IMBB researchers, to improve IMBB capacity for producing and analyzing scRNA-seq libraries*
- *Highly multiplexed 3'-quant-seq RNA-seq protocols (LEXOGEN UMI or QIAseq UPX) that enables economic low input/quality RNA samples (from few thousands of cells isolated by FACS) and output of confident Differentially expressed genes (DEGs) lists*
- *Set-up of pipelines for sequencing/data quality assessment/delivery of basic analyses to the users*

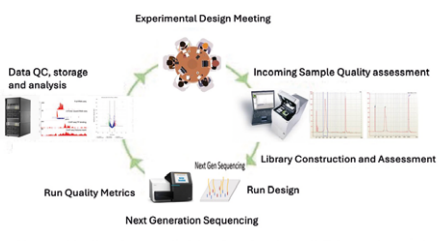
Coming soon

- *Streamlining and service of scRNA-seq libraries*
- *Implementation of sc-multiomics (scRNA-seq and sc ATAC-seq) services (with BD Rhapsody)*
- *Implementation of scRNA-seq pipelines to bioinformatics unit thanks to our TWINING grant to offer single-cell analyses to IMBB users in the near future*
- *Plan to develop long read sequencing services (LRS) to help IMBB researchers that are interested in full-length transcript and isoform analysis, or others in the discovery of new disease-causing variants*

Other activities

Participated in the workshops and annual meetings of the SCENTINEL consortium in Barcelona and Stockholm for Transfer of Knowledge of scRNA-seq protocols and analyses pipelines

Participated in researchers Night and Science Festival, in the 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.



Workflow at IMBB Genomics Facility and Bioinformatics Unit: from the scientist to the specialists and back

Web page https://www.imbb.forth.gr/imbb-people/en/genomics-facility-home
https://www.twinning-scentinel.eu/index.php/consortium/project-overview
https://www.imbb.forth.gr/en/facilities/Bioinformatics-Unit.15/&tabid=Overview.146

Publications by users lab Talianidis: Galanopoulou et al., Nat. Communications, 2024
Verginis: Semitekolou et al, iscience, 2025
Charalampopoulos: Chanoumidou et al., Biorxiv, 2025
Charou et al., Stem Cell Res. Ther., 2024
Kretsovali: Spanou et al., Stem Cell Reports, 2025
Kalantidis"Kallemi et al., Scientific Reports, 2024
Grypioti et al., New Phytol, 2024
Poulakakis:Psonis et al., FSIG, 2024
Kalpadakis (UoC): Efstratiou, Front .Med., 2025
Papdaki (UoC): Bizymi et al., Hemasphere, 2024
Gogas(NKUA): Palli et al., Front immun., 2025
Sarropoulou (HCMR): Saropoulou et al., Fish Shell. Imm., 2025
Papadaki et al., Gen and Comp. Endocrin., 2024

Giorgos Gouridis

Head Of Facility

PROTEOMICS FACILITY (PROFI)

Summary

Proteomics facility at IMBB (ProFI) is equipped with state-of-the-art mass spectrometry–based proteomics and bioinformatics tools, applying diverse workflows and developing new methodologies, particularly for the identification and characterization of proteins. ProFI's highly trained and experienced staff provide excellent research support and operate as a service facility for researchers within IMBB, as well as external academic and industrial laboratories. In 2024–2025, ProFI secured a major infrastructure upgrade through a regional (Periferia) funding action coordinated at IMBB by Prof. Vontas, enabling acquisition of an Orbitrap Excedion Pro high-resolution platform (installation expected April–May 2026), and is progressing toward a dedicated triple-quadrupole system for targeted SRM–MRM workflows via the CMBR-II infrastructure scheme.

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 2024-2025

- Completion of more than 15 submitted projects
- Projects of IMBB-users completed: Garinis, Kokkinidis, Moschou, Siden-Kiamos, Spilianakis, Tavernarakis
- Projects of Dpt. Chemistry-University of Crete completed: Neochoritis, Vassilikogiannakis
- Projects of external users completed: Varotsis (Cyprus University); Katharios (HCMR). ProFI (via the Gouridis group) strengthened its collaboration with HCMR by providing targeted proteomics support and analytical workflows for marine environmental samples, contributing to biomarker discovery and improved monitoring of ecosystem health.
- ProFI engagement in clinician-led, precision-medicine collaborations at the University of Crete (Medical School/Nephrology) together with the local SME SyNoesis Therapeutics, including the submitted CKD-IMPACT EU proposal (Cluster 1-Health) that integrates urinary complement proteomics with kidney-function measures and clinical-language analysis for actionable care and triage.

FACILITY MEMBERS

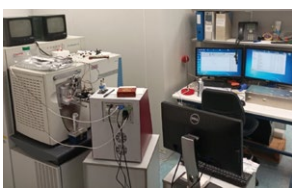
Special Research Assistant: Eirini Stratidaki

Facility Manager: Nikos Kountourakis

Facility Data Scientist / Bio-informatician: Kostas Tsolis

Other activities

- HFRI funded project completed at ProFI (Loukakos/IESL-FORTH)
- Major infrastructure upgrade secured: Orbitrap Excedion Pro (regional Periferia action coordinated at IMBB by Prof. Vontas; installation expected April–May 2026) and forthcoming triple-quadrupole MS for targeted SRM–MRM via CMBR-II.
- Collaboration with the Renal Clinic at the University General Hospital of Heraklion.



LTQ Orbitrap XL at ProFI

Orbitrap Excedion Pro Mass Spectrometer

Vanquish Neo UHPLC

Web page https://www.imbb.forth.gr/en/facilities/Proteomics-Facility-PROFI.12/&tabid=Facilities.105

Publications Divanach P, et al. (2025) FmocFF Peptide Hydrogel Is a Promising Matrix for Encapsulation and Controlled Release of the Anticancer Peptide Drug Bortezomib **Biomolecules**15(6):839

Tsakiri D, et al. (2025) Subcellular targets and recognition mechanism of Ralstonia solanacearum effector RipE1. **iScience** 28(5):112307

Katsara K, et al. (2024) Microplastics' Detection in Honey: Development of Protocols in a Simulation **Appl. Sci.** 14(11): 4720

Charalampos Pozidis

Head of the Unit

PROTEIN PURIFICATION FACILITY

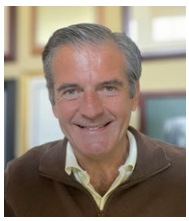
Protein Purification and Characterization Core Facility

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 2024-2025

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 https://www.imbb.forth.gr/en/facilities/Protein-Purification-Facility.8/&tabid=Members.65



Constantine A. Stratakis

Professor – RESEARCHER A'

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, personalizd 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.

EDIMO Unit of IMBB was established on 17/06/2022 by direct assignment from the General Secretariat for Research & Innovation (GRRI). The primary objective of EDIMO is to co-ordinate the activities of the Hellenic Precision Medicine Network (EDIMO) in terms of project organization, project management, strategic planning and quality control. The network is of pan-Hellenic scope and serves the needs of both patients and their families, as well as doctors and participating laboratories, clinics and hospitals. The network offers genetic/molecular oncology services and is the coordinating body for a range of research activities in the fields of precision medicine and oncology. The data collected from the services offered by the network are stored in databases and in turn lead to new research, diagnostic technologies and treatments in oncology.

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.

UNIT MEMBERS

Principle Staff Scientist: Dr. Emmanouela Linardaki
Post-Doctoral Researchers: Evmorfia Tzagkaraki, Elena Vorgia, Dionysia Petratou, Rodanthi Lyraki
Research Assistants (MSc): Polymnia Gkoumplia (Bioinformatics) (member until 31/12/2024)

Progress in 2024-2025

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

- Greek National Network of Precision Medicine in Cardiology and the Prevention of Sudden Death in the Young - EDIAK (icardiacnet.gr) (funded by research funds of the General Secretariat for Research and Technology of the Greek Ministry of Education - National Development Program): following the successful completion of the First phase of iCardiacNet, DIGENIA currently participates in the second phase of this program, iCardiacNet2. We have developed and validated an extended NGS panel of 159 genes linked to hereditary cardiovascular disease, and have analyzed over 100 clinical samples of patients and first and second degree relatives using either targeted NGS or Sanger sequencing.
- Brain Precision network (funded by research funds of the General Secretariat for Research and Technology of the Greek Ministry of Education): DIGENIA participated in a 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. So far we have analysed over 20 clinical samples using Whole Exome Sequencing.
- Hellenic Network for Precision Medicine in Molecular Oncology – EDIMO (www.edimo.gr) (funded by EU NextGenEU and the General Secretariat for Research and Innovation of the Hellenic Ministry of Development): EDMO unit is the coordinator the activities of EDIMO network, which up to 31/12/25 has facilitated the participation of >1330 oncology patients in this program and the referral of >1590 specialised cutting edge oncology biomarker analysis. DIGENIA unit has analyzed >125 clinical samples by NGS to identify predisposition to inherited syndromes causing endocrine tumors. In addition, >65 clinical samples have been analyzed for clinically significant somatic variants and tumor agnostic biomarkers, using a comprehensive molecular tumor profiling NGS methodology.
- Healthcare & Pharmaceutical Industry Transformation through Artificial Intelligence Digital Services – HEALTH-HUB (funded by NSRF 2021-2027): Health Hub supports a wide range of organizations and stakeholders interested in digital transformation and innovative health solutions, by offering a wide range of services as well as educational and supportive activities. DIGENIA offers Test-Before-Invest services to Diagnostic centers, hospitals, clinics, physicians, pharmaceutical and biotechnology companies, and research organizations developing applications in genetic analysis and precision medicine.

Other activities

- DIGENIA is part of the smartHEALTH European Digital Innovation Hub
- EDIMO received the 2025 Healthcare Business Gold Award for Development & Innovation (https://edimo.gr/vravefsi-tou-edimo-sta-healthcare-business-awards-2025/)

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

Publications Boumis P, et al. (2025). Huntington's Disease-like Syndrome as a Rare Presentation of CACNA1A-Related Disorder **Mov Disord Clin Pract.** doi: 10.1002/mdc3.70440, PMID: 41230709

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Σημαιάκης Γ, et al. Γενετικό τοπίο σειράς ασθενών με σποραδικό διαφοροποιημένο θυρεοειδικό καρκίνωμα (σπ-ΔΘΚ): νέες σωματικές αναδιατάξεις (Fusions) και η σημασία της αλληλούχισης νέας γενιάς (NGS) στη Μοριακή ανάλυση του όγκου και το σχέδιασμο της θεραπευτική στρατηγικής**. 52ο Πανελλήνιο Συνέδριο Ενδοκρινολογίας, Μεταβολισμού και Σακχαρώδη Διαβήτη,** 21-24 Μαίου 2025.

Grants

Grants

COMPETITIVE GRANTS AWARDED IN 2024-2025 (*Coordinator)

EU PROGRAMMES

ERA Chair-HORIZON-WIDERA-2023-TALENTS-01, InflaCare, Advance Inflammation Research at IMBB-FORTH, 2.500.000,00 €, 2025-2030, **G. Garinis***

ERC-2023-COG, PLANTEX, Limited proteolysis mechanisms in plants for selective protein translation to improve heat tolerance, 1.908.375,00 €, 2024-2029, **P. Moschou***

HORIZON-CL6-2023-FARM2FORK-01, NextGenBioPest, Next Generation Biopesticides for the control of the most "difficult-to-manage" pests and pathogens in fruits and vegetables, 1.024.375,00 €, 2024-2028, **J. Vontas***

HORIZON-CL6-2023-ZEROPOLLUTION, AquaBioSens, On-site biological sensing for aquatic pollutants and biohazards, 917.000,00 € (total grant budget: 2.470.992,50 €), 2024-2026, **E. Gizeli***

HORIZON-MSCA-2023-PF-01, LeVec, Molecular characterization of insecticide resistance and transmission competence in sand flies, major vectors of leismaniasis, 153.486,72 €, 2024-2026, **J. Vontas***

HORIZON-WIDERA-2023-ACCESS-02, SCENTINEL, Building Integrative single cell omics capacities using Invertebrate tumor models relevant to human disease, 747.907,50 € (total grant budget: 1.406.876,25 €), 2024-2027, **C. Delidakis***

HORIZON-WIDERA-2023-TALENTS-02-MSCA, POLAR, Phagosomal: LC3's Alternative Role, 169.326,72 €, 2024-2026, **G. Chamilos***

HORIZON-CL6-2024-FARM2FORK-03, EUFAWREADY, Enhancing Europe's readiness for managing fall armyworm, an invasive pest threat, 309.660,00 €, (total grant budget: 4.999.880,00 €), 2025-2029, **J. Vontas**

HORIZON-JU-GH-EDCTP3-2024-01, ResTick, Resilience Enhancement for Ticks and Tick-Borne Diseases in Sub-Saharan Africa, 1.187.500,00 € (total grant budget: 6.130.555,00 €), 2025-2028, **M. Kotsyfakis***

HORIZON-WIDERA-2023-ACCESS-07, DxHub, Connecting Greek and Portuguese Innovation Ecosystems to Develop a Hub for Infectious Diseases Diagnostic Solutions at the Point-of Care - Tackling Cross-border Threats», 1.055.000,00 € (total grant budget: 4.688.625,00 €), 2025-2028, **E. Gizeli***

HORIZON-WIDERA-2024-ERA-01, INCLUDE, Fostering INCLUsive biomedicine gender Equality plans in research and higher education institutions, 54.625,00 € (total grant budget: 999.889,75 €), 2025-2026, **A. Papoutsi**

HORIZON-WIDERA-2024-TALENTS-03, REENFORCE, Strengthening human capital and increasing the excellence of Widening-country organisations in R&I for bio-based, low-risk and smart Crop protection, 382.125,00 € (total grant budget: 2.998.048,75 €), 2025-2029, **J. Vontas**

GREEK PROGRAMMES

General Secretariat of Research & Innovation, iCardiacNet, Greek National Network of Precision Medicine in Cardiology and the Prevention of Sudden Death in the Young, 115.000,00 € (total grant budget: 3.000.000,00 €), 2024-2025, **C. Stratakis**

Hellenic Foundation for Research and Innovation, TraMeCaR, Dissecting the molecular mechanism and physiological role of Golgi-bypass as a major mechanism of subcellular protein trafficking, 99.660,00 €, 2024-2025, **G. Diallinas***

Hellenic Foundation for Research and Innovation, MAYA, Investigation of the protective roles of caloric restriction mimetics in myelin disruption via a novel, non-invasive advanced imaging approach, 200.000,00 €, 2024-2025, **D. Karagogeos***

Hellenic Foundation for Research and Innovation, APOE-META-BRAIN, Elucidating the impact of apolipoprotein E and metabolic comorbidities on the pathogenesis of Alzheimer's Disease, 210.800,00 €, 2024-2025, **D. Kardassis***

Hellenic Foundation for Research and Innovation, COFLEX, Mechanisms of cognitive flexibility across primates, rodents and machines, 200.000,00 €, 2024-2025, **P. Poirazi**

Hellenic Foundation for Research and Innovation-SNF, DENDROLEAP, A dendro-centric framework for learning optimization in biological and artificial systems, 1.250.000,00 €, 2024-2027, **P. Poirazi***

Hellenic Foundation for Research and Innovation, THESEUS, THe Genomics of the CrEtan population through hiStory and timE, shaping inflammation and immUne homeoStasis, 359.941,00 €, 2024-2025, **N. Poulakakis***

Hellenic Foundation for Research and Innovation, TRANSMOD, Modeling Transcription: an integrated approach to understand cancer-specific gene expression programs, 270.661,00 €, 2024-2025, **I. Talianidis***

Hellenic Foundation for Research and Innovation, GliaAge, Deciphering the role of glial autophagy in neurophysiology and ageing using in vivo chemo-optogenetics, 400.000,00 €, 2024-2025, **N. Tavernarakis***

Hellenic Foundation for Research and Innovation, NeuroFlame, Delineating the impact of DNA damage on Neuroinflammation during Aging, 125.000,00 €, 2024-2025, **N. Tavernarakis***

Hellenic Foundation for Research and Innovation, FIT, Deciphering the role of Cancer Associated Fibroblasts in immunotherapy resistance and tumor metastasis, 200.000,00 € (total grant budget: 321.800,00 €), 2024-2025, **P. Verginis***

Hellenic Foundation for Research and Innovation, MalVec, Improving the sustainability of malaria vector control, 280.000,00 € (total grant budget: 399.375,00 €), 2024-2025, **J. Vontas***

National Public Health Organization, Mosquito, Laboratory analysis of mosquitoes in the framework of enhanced entomological surveillance in the Prefecture of Crete for 2024, 13.728,00 €, 2024-2024, **J. Vontas***

Partnership Agreement 2021-2027, HEALTH HUB, EDIH for the transformation of the Health and Pharmaceutical sector through the use of AI digital services, 61.525,00 € (total grant budget: 2.915.857,00 €), 2024-2027, **N. Tavernarakis**

Region of Crete, Scientific support for mosquito control and the prevention of vector borne diseases in Crete, 69.700,00 €, 2024, **J. Vontas***

State Scholarships Foundation, HUBERT CURIEN, Regulation of the (patho)physiological adaptive immune response from SATB1 genome organizer, 10.000,00 €, 2024-2025, **C. Spilianakis***

Hellenic Foundation for Research and Innovation, AGELESS, A rheostat for cellular quiescence and aging, 299.902,00 €, 2025-2029, **P. Moschou***

Hellenic Foundation for Research and Innovation, NAREPIC, Unraveling the Nascent RNA Epitranscriptomic Control of Gene Expression in Cell Differentiation, 299.970,00 €,2025-2028, **E. Ntini***

Hellenic Foundation for Research and Innovation, WaveLimbShaping, High-resolution mechanistic analysis of allometric limb development with wavefront-shaping light-sheet microscopy, 299.970,00 €, 2025-2028, **A. Pavlopoulos***

Hellenic Foundation for Research and Innovation, MicroNerv, Microbial roots of the animal nervous system: homologs of neuronal molecular components in unicellular animal relatives and fungi, 60.424,23 €, 2025-2026, **A. Pittis***

National Public Health Organization, Mosquito, Laboratory analysis of mosquitoes in the framework of enhanced entomological surveillance in the Prefecture of Crete for 2025, 25.280,00 €, 2025-2026, **J. Vontas***

Region of Crete, CRINNA, Smart Tools, Infrastructure and Innovations for Improving the Quality and Safety of Agri-food Products in Crete, 899.868,00 € (total grant budget: 2.440.427,41 €), 2025-2027**, J. Vontas***

OTHER INTERNATIONAL PROGRAMMES

HFSP Research Grant, Exploring Interdisciplinary Frontiers to Understand Tick-Virus Dynamics at a Global Scale, 330.229,17 $ (total grant budget: 1.500.000,00 $), 2025-2028, **M. Kotsyfakis***

GATES FOUNDATION, NECTAR, Insecticide pharmacokinetics, 714.001,00 $, 2024-2027, **J. Vontas***

PRIVATE FUNDING

Fondation Santé, Vertebrate host homeostasis modulation by a tick salivary protein, 50.000,00 €, 2024-2026, **M. Kotsyfakis***

Fondation Sante, A mechanism safeguarding proteins getting stuck in solids, 50.000,00 €, 2024-2026, P**. Moschou***

HEVOLUTION FOUNDATION, Targeting genome stability as root cause of aging, 612.500,00 $, 2024-2028, **G. Garinis***

NAVAL, Harnessing protein biotechnology for synthetic biology, 16.445,00 $, 2024, **G. Gouridis***

University of Geneva, ANCIENT DNA, Antikythera shipwreck: integrated archaeogenomic and multi-isotope analyses of human skeletal remains and one olive pit, 63.250,00 €, 2024-2026, **N. Poulakakis***

University of Lausanne, ANCIENT DNA, Ancient DNA analysis of skeletal remains from Evia (Euboea), 50.000,00 €, 2024-2026, **N. Poulakakis***

Fondation Santé, Squaring the hexagon: cellular and molecular mechanisms mediating square cell packing in animal Epithelia, 25.000,00 €, 2025-2026, **A. Pavlopoulos***

Mass General Brigham, EPHYS-BWH, Studying CBD and GAT1508 synergy in epilepsy suppression, 60.200,00 $, 2025-2026**, K. Sidiropoulou***

REGENERON GENETICS CENTER LLC, WES of autoimmune disease cohorts in the Greek population, 298.683,98 $, 2025-2027, **G. Bertsias***

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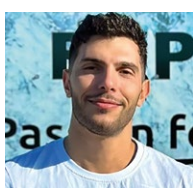

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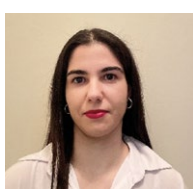

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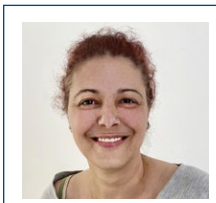

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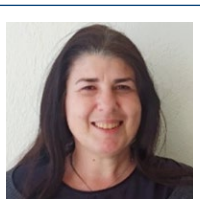

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BIENNIAL REPORT

2024-2025

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