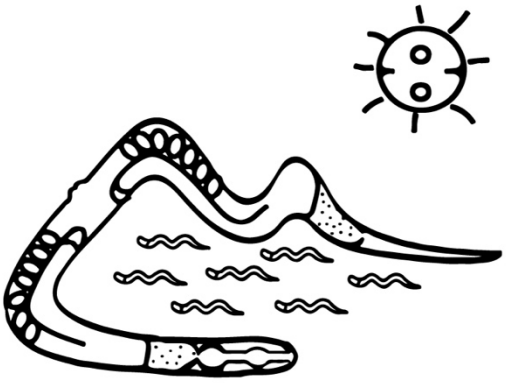

2nd MICeRCo Meeting

2.0nd Meeting of the Italian *C. elegans* Research Community (*M.I.C.e.R.Co.*)

Art Relais Palazzo Cappuccini, Naples

2-3 March 2023

Organizers

Elia Di Schiavi (IBBR), Simone Martinelli (ISS)

Scientific Secretariat

Pamela Santonicola, Giuseppina Zampi, Luca Pannone

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Welcome to the 2.0nd Meeting of the Italian *C. elegans* Research Community (M.I.C.e.R.Co.)!

After the success of the first meeting now several years ago and after the cancellation of the previous edition in 2020 due to the pandemic, we are pleased to announce the organization of the 2.0nd M.I.C.e.R.Co. that will be held in Naples on 2 and 3 March 2023.

The whole event will be organized in the Art Relais Palazzo Cappuccini in Napoli to facilitate the scientific interactions as much as possible. If it will be impossible to meet again in person, we will switch to online mode on the same dates.
Thanks to our sponsors we were able to offer 18 travel and 21 accommodation grants to young participants and thanks to Union Biometrica and Zeiss, two lectures will be given by Prof. Mario de Bono (Institute of Science and Technology Austria, ISTA, Vienna, Austria) and by Dr. Germano Cecere (Department of Development and Stem Cell Biology, Institut Pasteur, Paris, France).

The meeting is open to the participation of everyone interested and the official language of the congress will be English.

The main objectives of the meeting are:
• to favor the exchange of ideas, materials and information (on the example of small national meetings already held in Spain, France, United Kingdom and local meetings organized in the United States);
• to consolidate the Italian scientific community of *C. elegans* thanks to the interaction of Italian researchers working with *C.elegans*, both in Italy and in Europe;
• to allow researchers working with different models to be aware of the potential offered by *C.elegans* (whether they already collaborate or intend to collaborate) and give them the opportunity to present results or ideas for future collaborations;
• to give an opportunity to Italians working abroad with *C.elegans* to know and be known by those who work in Italy;
• to give young people the chance to present their data in an informal environment;
• to introduce the most advanced equipment and technologies from the *C.elegans* community.

See you soon!
Elia and Simone

BOOK OF ABSTRACT

LECTURES

INVITED LECTURE

A personal account of the beginning and early years of *C. elegans* research in Italy

PAOLO BAZZICALUPO

Naples, Italy

OPENING LECTURE SPONSORED BY ZEISS

A Complex Regulating Translation at the Neuronal Endoplasmic Reticulum

MARIO DE BONO

Institute of Science and Technology Austria, ISTA, Vienna, Austria

INVITED LECTURE SPONSORED BY UNION BIOMETRICA

Small RNAs in Epigenetic Inheritance

GERMANO CECERE

Department of Development and Stem Cell Biology, Institut Pasteur, Paris, France

TALKS[1]

[1]Abstracts are listed in alphabetical order by presenting author's last name.

Characterization of a new *C. elegans* model for Wilson disease studies

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Copper is a vitality nutrient in the human body, important for many biochemical processes and for normal growth, development, and health. However, excess of copper represents a danger, due to its ability to induce free radical-induced oxidative damage, lipid metabolism and neuronal activity impairments. Wilson disease (WD) represents an excellent system for Cu toxicity studies, since is caused by mutations in ATP7B, which is involved in effluxing excess Cu from hepatocytes into the bile. Loss of ATP7B leads to Cu overload in liver and then in the brain, causing fatal hepatic and neurologic abnormalities.

C. elegans has emerged as a model to study micronutrient metabolism; for this reason, we focused our attention on the characterization of a WD model in C. elegans upon copper treatment. CUA-1, the *C. elegans* homolog of ATP7B, is localized into lysosome-like organelles in the intestine in presence of excess of copper and is a key component regulating copper supply and detoxification to maintain copper homeostasis.

H1069Q is the most common mutation of ATP7B in northern European populations and we obtained and characterized a cua-1(H828Q) mutant strain through CRISPR/CAS9 technology. Our studies revealed that in absence of Cu, cua-1[H828Q] strain does not show any significant phenotypic aberrations. However, mutant worms exhibited very poor resistance to Cu compared to the control strain. This manifested in a strong decrease in number of eggs, a delay in the larval development, a shorter lifespan, impaired motility, and mitochondrial damage. Further investigation of WT and H828Q variants suggest that mutant cua-1 is subjected to retention and degradation in the ER like human ATP7B-H1069Q mutant. We further plan to use this model for identification and validation of the new therapeutic targets for WD.

Keywords: Wilson, *cua-1*, copper.

Molecular targets of nematicidal activity of essential oils

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The use of essential oils (Eos) and their components in the formulation of nematicide products with reduced environmental impact is gaining increasing interest both in the scientific and industrial fields. This study aimed to determine the mechanism of action of OEs at level of phenotype and their effects on the expression levels of four gene targets involved in the motility and protection mechanisms of the root-knot nematode *Meloidogyne incognita*. Infective second stages of *M. incognita* were incubated for 2 and 4 hours with sublethal doses of two EOs with different nematocidal activity, such as *Cynnamomum zeylanicum* and *Citrus aurantium*, and then observed at the microscope for the phenotype. Real time PCR was used to determine the expression level of the gene targets as acetylcholinesterase *ace*-1 and *ace*-2 (motility of nematode), *hsp*90 (response to biotic and abiotic stress), and fatty acyl-CoA reductase-1 (*far*-1, cuticle protection). The obtained on the nematicide activity of both Eos will be presented.

Keywords: essential oil, nematicide, real time PCR.

G-protein coupled receptors as potential therapeutic targets in movement disorders/epilepsy caused by *GNAO1 de novo* mutations

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Dominant mutations in the *GNAO1* gene underlie a severe neurological condition characterized by hyperkinetic movement disorders, epilepsy, developmental delay, and cognitive decline, with infantile/childhood onset. *GNAO1* encodes the α-subunit of an inhibitory G-protein regulating ion channel activity and neurotransmitter release. The pathogenic mechanisms underlying *GNAO1*-related disorders remain largely elusive and to date there are no effective therapies. Here, we generated CRISPR-Cas9-engineered *C. elegans* strains harboring four pathogenic variants in *goa-1*, the *C. elegans* orthologue of *GNAO1*, associated with diverse clinical features. Like null mutants, homozygous knock-in animals showed increased egg laying and were hypersensitive to aldicarb, an inhibitor of acetylcholinesterase, suggesting excessive neurotransmitter release by different classes of motor neurons. Automated analysis of *C. elegans* locomotion indicated that *goa-1* mutants move faster than control animals, with more frequent body bends and a higher reversal rate, and display uncoordinated locomotion. Phenotypic profiling of heterozygous nematodes revealed a mutation- and cell-specific dominant-negative behavior of the mutant alleles. In a pilot drug screening performed with compounds targeting G-protein coupled receptors (GPCRs), caffeine and istradefylline, an FDA-approved drug in the treatment of Parkinson's disease, were found to rescue the hyperactive motor behavior of *goa-1* mutants, by blocking, at least in part, a putative adenosine receptor in the nematode. Moreover, knocking-down the expression of GPCRs playing a role upstream to stimulatory G-proteins by RNAi reduced the locomotion defect of *goa-1* mutants. Overall, our findings establish *C. elegans* as an efficient drug-screening platform for *GNAO1*-related disorders and highlight the potential role of GPCRs modulation in controlling dyskinesia.

Keywords: movement disorders, *goa-1*/*GNAO1*, GPCRs.

Conserved functions of mouse ARX and *Caenorhabditis elegans alr-1* in controlling pathways damaged in neurodevelopmental disorders (NDDs)

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The X-linked *ARX* gene encodes the Aristaless-related homeobox protein, which is a morphogenetic transcription factor with a crucial role in cerebral development and patterning. Mutations in *ARX* cause a wide spectrum of X-linked neurodevelopmental disorders affecting male children, as lissencephaly with abnormal genitalia (XLAG), which is a severe cortical malformation, and developmental and epileptic encephalopathy type 1 (DEE-1), a severe paediatric epilepsy characterized by recurrent and pharmaco-resistant seizures. Here we describe the conservation of multiple ARX-dependent disease-pathways among human, mouse and nematode establishing a gene-phenotype association from one organism to another. Starting from the homologous gene relationship between *ARX* and its murine (*Arx)* and worm (*alr-1)* counterparts, we discovered that the activity of the epigenetic ARX-KDM5C axis and the organization of microtubule cytoskeleton are conserved functions deeply damaged in XLAG mice and *C. elegans* mutants, respectively ablated for *Arx* and *alr-1*. Furthermore, abnormal alternative splicing (AS) repertoires in *Neurexin-1*, a gene encoding multiple pre-synaptic organizers implicated in synaptic remodelling, were detected in the epileptogenic brain areas and in the depolarized cortical neurons of DEE-1 *Arx* mice and in the *alr-1*(KO) animals. We also proved the ability of the epidrug Vorinostat to rescue ARX/alr-1 dependent phenotypes both in murine and *C.elegans* KO mutants. Given the complexity of the regulatory network controlled by ARX, mouse and worm studies offered a powerful experimental strategy that allowed us to identify unanticipated evolutionarily conserved regulatory circuits and to improve our knowledge on the pleiotropic activity of ARX, both at the cellular and tissue levels.

Keywords: Arx-related diseases, mouse and *C. elegans* mutants, epi-drug treatments.

Towards healthy ageing: Investigating the regulation of extracellular protein aggregation

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Accumulation of protein aggregates is an inherent part of normal ageing in numerous organisms. Protein aggregation with age affects the proteome of different tissues, cellular compartments as well as in the extracellular space. Age-dependent protein aggregates contribute to functional decline and thus are prime targets in the search of strategies to promote healthy ageing. Compared to the relatively constant intracellular environment, conditions for proteins in the extracellular space are harsher and low ATP concentrations preclude activity of the intracellular protein-quality-control components. Until now, only a few bona fide extracellular chaperones and proteases have been shown to limit extracellular protein aggregation. Here, we have uncovered the extracellular proteostasis network that regulates protein aggregation outside of the cell in *C. elegans*. We discovered 57 regulators of extracellular protein aggregation, including several proteins related to innate immunity. Promoting extracellular proteostasis can prolong lifespan and, notably, extracellular proteostasis components are up-regulated during the innate immune response to enhance survival. Mimicking a pathogenic attack, we found that *C. elegans* responded by increasing the expression of components of extracellular proteostasis and by limiting aggregation of extracellular proteins. Together this work reveals mechanisms used by the organism to protect its proteome against aggregation and highlights intriguing connections with the response to pathogens.

Keywords: proteostasis, aging, immunity response.

See Elegans: simple-to-use, accurate, and automatic 3D detection of neural activity from densely packed neurons

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Thanks to its genetic tractability, compactness, and the optical accessibility of its nervous system, the nematode *Caenorhabditis elegans* provides an outstanding platform for systems neuroscience. Recent advances in neural technologies and novel methods to record and characterize the neural dynamics from large portions of the nervous system make the emerging field of whole-brain techniques with single-cell resolution the new frontier to investigate the link between brain activity and behavior.
In *C. elegans*, whole-brain recordings consist of a time series of volumes that need to be processed for neuronal trace extraction. Here, we propose See Elegans: a direct programming algorithm that combines different techniques for automatic neuron segmentation and tracking, and we compare it with other available algorithms. While outperforming them in most cases, our solution also offers a novel method to guide the identification of a subset of the nematode head neurons. The built-in interface allows the user to follow and hand-curate each of the processing steps. See *Elegans* is thus a simple-to-use interface aimed at speeding up the post-processing of volumetric calcium imaging recordings while maintaining a high level of accuracy.

Keywords: whole-brain imaging, calcium imaging.

C16ORF70, A Novel Gene that Regulates Aging in *C. elegans*

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This abstract is not available online on request of the presenting author.

C. elegans recognizes as toxic tau oligomers

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Abnormal Tau phosphorylation and aggregation into bundles of filaments in the central nervous system is a common feature of a heterogeneous group of pathologies called Tauopathies. Similarly to other misfolded proteins, Tau oligomers, more than fibrillar assemblies, have been suggested to be the main responsible for toxicity.

With the hypothesis that abnormal Tau conformers play a causal role in driving toxicity, we conceived an original, integrated approach involving recombinant human Tau, cells overexpressing P301L-mutatedTau (TauP301L), brain homogenates from transgenic mice overexpressing TauP301L, and *C. elegans*. Cerebral homogenates from traumatic brain injured (TBI) mice were also employed as an additional preclinical model of Tauopathy.

We found that Tau oligomers, particularly trimeric and tetrameric assemblies, specifically induced a functional deficit in *C. elegans* consisting of neuromuscular impairment and altered synaptic transmission. A similar toxic effect was observed in worms exposed to brain homogenates from P301L or TBI mice, proving that *C. elegans* represents a tractable model to investigate Tau toxicity *in vivo*.

We next evaluated the applicability of this worm-based approach for testing compounds acting against oligomeric Tau toxicity. To this end, we employed doxycycline as a prototypic anti-amyloidogenic drug. Doxycycline was able to protect worms from the toxicity induced by Tau, inhibiting the formation of Tau oligomers.

Keywords: Tau, Tauopathy, Toxicity.

Mechanosensory abilities of the AWCon chemosensory neurons

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AWCon chemosensory neurons are critical for *C. elegans* life and behavior, being responsible for detecting volatile attractive odorants. In this work, we report a novel ability of these neurons to detect mechanical stimuli caused by fluid flow changes in a microfluidic device. AWCon mechanical responses differ in shape from chemosensory ones, displaying a plateau-like behavior suggesting a bistability in the intracellular calcium dynamics that persists over a long time. We investigate the mechanosensory behavior with a combination of microfluidic technology and calcium imaging experiments on selected mutant worms. Experiments performed in a shearless microfluidic device suggest that AWCon neurons are sensitive to the tangential component of mechanical stress rather than hydrostatic pressure changes. We also showed that these responses might have an intrinsic origin, as suggested by tests on *unc-13(e51)* and *unc-31(e928)* mutants. Moreover, our results on the *tax-4(ok3771)* mutants highlight the critical role of CNG-gated channels in the mechanical responses, suggesting that these responses might recruit the GPCRs signaling pathway.

Keywords: AWCon, mechanosensation.

spa*Ce*: assessing relative biological effectiveness of simulated deep space radiation in altering neural function and survival in *C. elegans*

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This abstract is not available online on request of the presenting author.

Modeling RASopathies in *C. elegans*: a long-lasting story

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Enhanced signaling through RAS and the mitogen-associated protein kinase (MAPK) cascade underlies the RASopathies, a family of clinically related disorders affecting development and growth. In *C. elegans*, signaling through *let-60*, homolog of the *HRAS*, *KRAS* and *NRAS* genes, and the MAPK cascade, plays a fundamental role in vulval development, making it an excellent model to decipher the molecular mechanisms and to identify novel candidate genes. Since 2009, we have generated multiple models of these diseases. Heat-shock-mediated overexpression of SHOC2 and RRAS mutant alleles demonstrated their gain-of-function (GOF) effect on RAS signaling controlling vulval induction and the aberrant migration of vulval precursor cells through dysregulation of the small GTPases RAC1 and CDC42, highlighting a possible role of these proteins in the pathogenesis of RASopathies. Consistently, we identified *CDC42* as a new disease-causing gene underlying a heterogeneous group of developmental disorders within the phenotypic spectrum of RASopathies. More recently, we used vulval-specific overexpression of 12 *MAPK1* NS- and cancer-causing mutations to evaluate their GOF role and correlate it to the phenotype. Finally, we have recently generated a CRISPR-Cas9-edited strain harboring the most common variant associated with Costello syndrome in order to characterize non-vulval phenotypes, including longevity, oxidative stress, and neuromuscular defects. Overall, our data established *C. elegans* as a powerful tool for studying the pathogenic mechanisms underlying RASopathies.

Keywords: RASopathies, vulval development, RHO-GTPases.

Immunoglobulin light chain amyloidosis modelled in *C. elegans*

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This abstract is not available online on request of the presenting author.

hrpr-1 rescues SMA-related neurodegeneration by modulating *ret-1* splicing

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Correct mRNA splicing is required in all cells, but neurons seem more vulnerable to splicing perturbations. In fact, numerous neurodegenerative diseases are caused by splicing defects, such as Spinal Muscular Atrophy (SMA). SMA is mainly caused by mutations in the Survival Motor Neuron (*SMN1*) gene, which is involved in RNA metabolism and splicing. To better clarify the relationship between splicing and neurodegeneration, we performed an RNA-sequencing of motoneurons derived from induced pluripotent stem cells (iPSCs-MNs) from SMA patients and healthy people, and identified differentially expressed/spliced genes, which were enriched in RNA motif 7. This motif is specifically recognized by hnRNP Q, a spliceosomal component physically interacting with SMN. We demonstrated that *hrpr-1,* the hnRNP Q homolog in *C. elegans*, is an essential gene involved in neuronal survival. In fact, *hrpr-1* depletion*,* similarly to *smn-1* depletion, causes larval arrests, reduction in the lifespan, locomotion defects and neurodegeneration. We confirmed *hrpr-1* and *smn-1* genetic interaction in MNs, by nonallelic noncomplementation and by rescuing *smn-1* related neurodegeneration through *hrpr-1* overexpression in MNs. By comparing *hrpr-1* known targets in *C. elegans* and the alternatively spliced gene identified in iPSCs-MNs from SMA patients, we identified a new downstream target, *ret-1/RTN*. We observed alteration in *ret-1* splicing pattern when *smn-1* is depleted and that *ret-1* mediates *hrpr-1* rescue of *smn-1* related neurodegeneration*.* Interestingly, *ret-1/RTN* role in SMA is conserved, since we observed that RTN transcript levels are altered in SMA mice and iPSCs-MNs from SMA patients. We demonstrated, for the first time, the neuroprotective role of *hrpr-1* and we identified *ret-1* as new potential therapeutic target for SMA.

Keywords: neurodegeneration, alternative splicing, SMA.

2-hydroxyisobutyric acid (2-HIBA) modulates ageing and fat deposition in *Caenorhabditis elegans*

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High levels of 2-hydroxyisobutyric acid (2-HIBA) were found in urines of patients with obesity and hepatic steatosis, suggesting a potential involvement of this metabolite in clinical conditions. The gut microbial origin of 2-HIBA was hypothesized, however its actual origin and role in biological processes are still not clear. We investigated how treatment with 2-HIBA affected the physiology of the model organism *Caenorhabditis elegans*, in both standard and high-glucose diet (HGD) growth conditions, by gene expression and metabolomic analyses, Coherent Anti-Stokes Raman Scattering (CARS) and two-photon fluorescence microscopy. In standard conditions, 2-HIBA resulted particularly effective to extend the lifespan, delay ageing processes and stimulate the oxidative stress resistance in wild type nematodes through the activation of insulin/IGF-1 signaling (IIS) and p38 MAPK pathways and, consequently, through a reduction of ROS levels. Moreover, variations of lipid accumulation observed in treated worms correlated with transcriptional levels of fatty acid synthesis genes and with the involvement of peptide transporter PEP-2. In HGD conditions, the effect of 2-HIBA on *C. elegans* resulted in a reduction of the lipid droplets deposition, accordingly with an increase of *acs-2* gene transcription, involved in β-oxidation processes. In addition, the pro-longevity effect appeared to be correlated to higher levels of tryptophan, which may play a role in restoring the decreased viability observed in the HGD untreated nematodes.

Keywords: 2-hydroxyisobutyric acid, ageing, lipid metabolism.

C. elegans-based chemosensation strategy for the early detection of cancer metabolites in urine samples

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Chemosensory receptors play a crucial role in distinguishing the wide range of volatile and soluble molecules in the environment, by binding them with high accuracy. Chemosensation is the main sensory modality in organisms lacking long-range sensory mechanisms like vision and hearing. Despite its low number of sensory neurons, the nematode *Caenorhabditis elegans* possesses several chemosensory receptors, allowing it to detect about as many odorants as mammals. In this work, we show that *C. elegans* displays attraction towards urine samples of women with breast cancer while avoids control ones. Behavioral assays on animals lacking AWC sensory neurons demonstrate the relevance of these neurons in sensing cancer odorants. The accuracy of this discrimination, increases up to 97.22% when performing calcium imaging experiments on AWC neurons. Also, chemotaxis assays on animals lacking GPCRs specifically expressed in AWC allow to identify receptors involved in binding cancer metabolites, suggesting that *C. elegans* may be of help identifying a metabolic fingerprint of breast cancer.

Keywords: Olfactory receptors, Breast cancer.

Cocoa Polyphenols as Functional Food to counteract the Spinocerebellar Ataxia Type 3 disease

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Spinocerebellar Ataxia Type 3 (SCA3) is an incurable neurodegenerative disease caused by an abnormal expansion of the polyQ track present in the C-terminal of the ATX3 protein. It is the second polyQ disease for incident worldwide and its principal hallmark is a progressive ataxia. The onset of the SCA3 occurs when the ATX3 polyQ track exceeds the threshold of 55 glutamines (ATX3Q55), causing ATX3 aggregation and leading to the formation of intra-neuronal aggregates and amyloid fibrils.

One of the possible therapeutic strategies is based on the discovery of compounds capable to counteract the ATX3 aggregation. Cocoa seeds from *Theobroma cacao* are a rich source of polyphenols and, thanks to its delicious flavours and world diffusion; it can be used as powerful functional foods.

Firstly, we assayed in vitro the anti-aggregation proprieties of the polyphenols enriched fraction of cocoa (CP) seeds on ATX3Q55 aggregation by Thioflavin T assay, solubility test, and Atomic Force Microscopy analysis, finding that CP affectes ATX3Q55 aggregation. Moreover, we used our *Caenorhabditis elegans* SCA3 model to assess the beneficial effect of CP. We daily fed nematodes with 0,5 mg/ml CP from the first day of adulthood and we observed an increase in the mean lifespan from 3 to 7 days, and an increase of 20% in body bands numbers, with respect to the untreated nematodes and to the control strain expressing a non-pathological ATX3 variant.

Our results support the cocoa polyphenols employment as a potential functional food to contrast the SCA3 development.

Keywords: SCA3, functional food.

Characterization of the transgenic animal models *Danio rerio* and *Caenorhabditis elegans* to examine pathophysiology associated with *SMARCB1* variants

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SMARCB1 is an ubiquitously expressed nuclear protein and a core subunit of the BAF chromatin-remodeling complex. *SMARCB1* variants have been associated with different diseases including tumor predisposition syndromes (Rhabdoid Tumor Predisposition Syndrome RTPS1 and Schwannomatosis) and developmental disorders (Coffin-Siris Syndrome).

In this project, we propose to develop and characterize two transgenic animal models, *Caenorhabditis elegans* and *Danio rerio*, to examine the pathophysiology associated with *SMARCB1* variants.

In both model organisms we analyzed the spatial and temporal expression of *SMARCB1* orthologues during development. In *D. rerio* there are two paralogs: *smarcb1a* and *smarcb1b*; the two isoforms were detected from the first stages of the embryonic development and also in all tissues. With an *in-vivo* analysis, we observed that *smarcb1* reaches the highest levels of expression in the central nervous system, highlighting a central role in this context. In *C. elegans* instead, the single isoform *snfc-5* is expressed from the egg stage to the adulthood. Together our findings suggest that *smarcb1* is a maternal determinant in both species.

With CRISPR/Cas9, we obtained *smarcb1a-/-, smarcb1b-/-* and *smarcb1ab+/-* in *D. rerio*: the knock-out lines will be phenotypically characterized. In *C. elegans* instead, were obtained three independent lines harboring mutations associated with distinct human phenotypes. The lines of both model organisms will be employed to analyze the molecular pathways related to the BAF complex in order to clarify the poorly understood mechanisms of *SMARCB1* variants pathogenesis.

Hopefully, the integration of all this multidisciplinary approach could help us to identify novel therapeutic targets for the future.

Keywords: *SMARCB1*, model organisms.

Mitochondria hormesis in neuromuscular pathologies: an organismal perspective from development to aging

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Organisms' development and aging are seemingly opposing processes and, as such, their associated pathologies are primarily tackled by different fields. Recent studies are however challenging this dogma. The recognition of a functional interplay between development and aging may help gaining new insight into pathomechanistic aspects of relevance for therapeutic strategies for different disorders over the entire lifespan. In particular, while mitochondria dysfunction is one of the hallmarks of aging and severe mitochondrial deficiency lead to neuromuscular diseases, mild mitochondrial stress during development promotes *C. elegans* healthy aging (mitohormesis). We investigated mitochondrial stress responses (MSR) possibly underlying these effects (i.e. different forms of cell death such as autophagy, apoptosis, ferroptosis) and showed that mitochondrial (dys)function during development predicts animals' health-span. Of note, we exploited the very reproducible, discrete and automatically quantifiable parameters associated with mitohormesis in *C. elegans,* for phenotype-based high-content screening in search of compounds promoting healthspan. In support of a clear interplay between developmental- and age-related processes, our screens led to the identification of pro-longevity compounds activating MSR early in life (e.g. Lutein), which we could also use to counteract inborn mitochondrial disorders. Remarkably, we uncovered a synaptic protein, neuroligin, that mediates the beneficial effects of Lutein in both development and aging contexts, yet in opposite directions. We speculate neuroligin may function as a cellular rheostat in response to different degrees of mitochondrial stress in turn modulating neuromuscular fitness in a context-dependent manner.

Keywords: aging, development, mitochondria-associated neuropathologies.

Reverse genetic screen of Parkinson's disease-susceptibility genes identifies novel modulators of alpha-synuclein neurotoxicity in *C. elegans*

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Neurotoxicity of alpha-synuclein (aSyn) is a pathogenetic hallmark of synucleinopathies, including Parkinson's diseases (PD). Only about 10% of diagnosed Parkinson's disease (PD) have familial history with identified genetic variations, while pathogenetic triggers in sporadic forms of PD are largely unknown. Genome-wide association studies over recent years have revealed approximately 90 risk genetic loci associated with developed PD. To date, however, there is little to no functional validation of genes in these loci. In this study, we performed reverse genetic screening of some of these candidate risk genes, looking for modulated toxicity of aSyn in dopaminergic neurons of *C. elegans*. We generated *C. elegans* PD model expressing GFP-tagged aSyn in dopaminergic neurons, which forms aSyn inclusions and triggers neurodegeneration in aged animals. Using RNA interference, we targeted *C. elegans* orthologs of 100 human risk genes for PD from the published GWAS loci and identified knockdown animals with exacerbated or alleviated aSyn-induced neurodegeneration. We show that several genes regulating calcium signalling modulated aSyn toxicity in dopaminergic neurons and conclude that the genes regulating import of calcium into mitochondria are potential therapeutic targets for PD.

Keywords: Neurodegeneration, Parkinson's disease.

POSTERS[1]

[1]Abstracts are listed in alphabetical order by presenting author's last name.

Analysis of inhibitory effects of dietary delivered Self-DNA in *Caenorhabditis elegans*

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All organisms, from bacteria to mammals, sense and respond to foreign nucleic acids to fight infections in order to survive and preserve genome integrity in all types of invaded cells.

As part of the immune response, specific molecular pathways are activated to sense both foreign DNA and damaged or aberrantly localised self-DNA inside the cell.

To avoid unwanted responses to regular physiological processes, recognition of endogenous nucleic acids is actively regulated by the cells and alteration of such mechanisms is associated with various diseases.

We investigated the effects of dietary delivered self-DNA in the nematode *Caenorhabditis elegans*. The hermaphrodite worms were fed on *Escherichia coli* genomic libraries: a *C. elegans* library (self) and a legume (*Medicago truncatula*) library (non-self). The presence of self-DNA in the food significantly decreases egg deposition, induced high embryo death, and negatively affected larval development. DNA damage and activation of p53/CEP-1-dependent apoptosis occur in gonadal germ cells.

The genetic tractability of *C. elegans* will help to identify the basic molecular pathways involved in such mechanisms.

The observed phenomenon suggests possible applications for the biocontrol of parasitic nematodes by appropriate delivery of their self-DNA in their growing environment.

Keywords: Self-DNA, DNA damage.

Semi-automated screening of drug-libraries to identify neuroprotective compounds in a *C. elegans* model of SMA.

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Spinal muscular atrophy (SMA) is a neurodegenerative disease caused by mutations in the survival motor neuron gene (*Smn1*). In the last years three different drugs have been approved by FDA for SMA treatment, nevertheless they resulted to be not efficacious for all the type of SMA patients. So, to identify potential therapeutic molecules to be used in combination with actual treatments, we took advantage of our *C. elegans* SMA model, where *smn-1,* the *Smn1* ortholog, is specifically silenced in motoneurons (MNs), causing an age-dependent neurodegeneration. We successfully used this model for an unbiased semi-automated high conten imaging (HCI) drug screening of an FDA-approved library, that allowed us to analyse 384 compounds/week in triplicate. By using this approach, we identified four new exciting leading compounds counteracting *smn-1* related neurodegeneration in *C. elegans.* One of these was discarded after the secondary screening, while another, Pimozide, is a compound recently published to be effective in another SMA model in *C. elegans*, thus strongly supporting the efficacy our approach. We are now expanding the screening to other libraries, determining the dose-response curve and the time of action of these compounds, as well as their mechanisms of action. Our results demonstrate that we are able to isolate pharmacological hits that suppress MNs degeneration by combining *in vivo* high content imaging with drug screening approaches, delivering major progresses in defining new treatments for preventing the neuronal death caused by *smn-1* loss in *C. elegans* motoneurons.

Keywords: neurodegeneration, drug screening, SMA.

Unraveling TBP/TBP-1 and CHIP/CHN-1 interaction in *C. elegans*: a plan to model a digenic disease

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Spinocerebellar ataxias type 17 (SCA17) and type 48 (SCA48) are both characterized by cerebellar-cognitive-behavioural features and incomplete penetrance. While SCA17 is caused by a CAG/CAA (polyQ) repeat expansion in the *TBP* gene, with full penetrance for alleles with >49 repeats and reduced penetrance for intermediate 41-49 alleles, SCA48 is attributed to heterozygous pathogenic variants in the S*TUB1* gene. We recently demonstrated a digenic inheritance of the *STUB1*/*TBP* genotype which explains the incomplete penetrance in SCA17 and SCA48, showing that SCA17 is a monogenic disorder for TBP expansions with >47 polyQ and a "true digenic" *TBP*/*STUB1* disorder (SCA17^{digenic}) for intermediate TBP alleles (41-46 polyQ). *TBP* encodes the TATA-Box Binding Protein, a transcription factor that binds the majority of promoters. *STUB1* encodes CHIP, an E3 ubiquitin ligase with a cochaperone activity that mediates the proteasomal degradation of misfolded proteins. Notably, in SCA1, SCA3 and Huntington's disease animal models, suppression of CHIP activity worsened the severity of the phenotype and the polyQ protein aggregation, suggesting that CHIP may play a role in the degradation of TBP.

To unravel the nature of TBP-CHIP interaction, we are currently modeling SCA17 and SCA17^{digenic} in *Caenorhabditis elegans* which has orthologs for both *TBP* and *STUB1* named *tbp-1* and *chn-1*, respectively, whose functions are conserved. *C. elegans* SCA17 models expressing human alleles with 38 repeats (wild-type), 43 repeats (intermediate) and 54 repeats (fully-penetrant) will be generated and phenotypically characterized. Finally, TBP/CHN-1 interaction will be investigated crossing these SCA17 models with *chn-1* mutant animals (FRRB-CP-20/2018 to FT).

Keywords: SCA17, digenic interaction, *CHIP*/*CHN-1*.

Nutraceutical approach to improve elderly health: aging phenotypes characterization in *Caenorhabditis elegans*

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One of the main challenges of the 21st century is the aging of the population, since the ratio of elderly people is progressively increasing. Aging is considered a huge problem because it consists in a gradual physiological decline and represents a risk factor for several pathologies. Understanding the mechanisms underlying aging is fundamental to promote healthy aging, even if it is complicated by its multifactorial nature, in which environmental factors (e.g. nutrients) play an important role. *Caenorhabditis elegans* is a validated model for aging research, thanks to its short life cycle, easy manipulation and evolutionarily conserved pathways.

In this work, the main aging phenotypes have been analyzed. Since *C. elegans* early adulthood, we observed a progressive decline of both movement and pumping rate during lifespan. Otherwise, the heat stress resistance decreases only in old age. This leads to suppose that the first two parameters could be modulated by the same pathways, unlike the heat stress resistance.

Given the important impact of diet on healthy aging, the effect of the *Cinnamomum cassia* buds extract (rich in polyphenols) on *C. elegans* lifespan has been evaluated. The most effective dose has been defined by heat stress test, pre-treating adult worms with a single dose for 48 hours. We observed that the treatment with the most effective dose during *C. elegans* development slightly increases median and maximum lifespan. The next step will be to analyze the effect of the extract on the healthspan parameters.

Keywords: Aging, Nutrients.

Development of functionalized masks: improvement of personal protective equipment using nanomaterials

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The microbiological contamination of surfaces in the healthcare sector remains an issue of great concern for public health. Pathogens can persist in such environments and spread through healthcare personnel and patients, or simply through contact with contaminated surfaces and equipment. In an era of increasing antibiotic resistance, it is becoming very difficult to fight infectious diseases, resulting in serious morbidity and mortality in the healthcare sector. Recently, the SARS-CoV-2 pandemic has significantly increased the use of wear of surgical masks; despite this, the possibility of bacterial infection becomes very high, because of people removing their masks and then putting them back later, such as when eating and sweating; they create a suitable environment for bacteria to grow.

The biological and biomedical fields became the most important application areas of nanotechnology. Indeed, one of the advanced characteristics of nanomaterials (NMs) is their antimicrobial properties. The power of NMs as antimicrobial agents is widely studied and is being tested as an alternative method to overcome the challenges resulting from bacterial multidrug resistance. To the final aim to achieve the creation of personal protective equipment with antimicrobial activities, through functionalization with Graphene Nanoplatelets (GNPs), possible toxic effects exerted by these nanomaterials were evaluated on *Caenorhabditis elegans* animal model. Indeed, its several advantages make nematode a very suitable model for nanotoxicology studies. We evaluated *in vivo* biocompatibility, to test adverse effects of GNPs eventually detached from the engineered mask surface, through analysis of lifespan, fertility and aging.

Keywords: biocompatibility, Graphene Nanoplatelets, mask.

Procedurally generated training sets for deep learning-mediated semantic segmentation in *C. elegans* behavioral analysis

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Convolutional neural networks are the state-of-the-art in image segmentation and deliver accurate and robust segmentation of target structures. The training of these networks requires significant amounts of labeled training data that often precludes their use. However, applying deep learning on image analysis greatly enhances high-throughput analysis of motion, egg-laying, feeding, chemotaxis, etc. Here, we propose a method that procedurally generates any number of labeled training images without the need of user labeling. We use a simple, parameterized, and geometric model of the roundworm to generate a highly variable dataset by randomization. Through parameterization of animal geometry, movement, and background, we generate training data that match the user's microscopic images. Training deep learning algorithms with these artificial training sets then results in accurate segmentation of the structure-of-interest. Together, we provide a framework for automatic labeling and tracking of anatomically discernible landmarks such as head, tail, pharynx, vulva, gut, eggs, and gonads. Our approach will make deep-learning more accessible to experimentalists and significantly reduce the time required for building robust training sets.

Keywords: quantitative analysis, behavior, deep learning.

Exploitation of the Bio-MEMORY collection CNR-IBBR CeLITABASE for the characterization of highly conserved molecular pathways involved in neurodevelopmental disorders (NDD)

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Neurodevelopmental disorder (NDD) genes play a role across a range of biological functions, including transcriptional regulation, epigenetic modification, and synaptic structure and functioning. Although NDD genes are functionally diverse, they are highly inter-connected and control multiple processes, including neuronal morphology, synaptic plasticity and neuronal homeostasis. In this framework, the identification of secondary molecular determinants contributing to disease phenotypes is essential for dissecting the pathogenetic mechanisms. Given the intricate disease network at the basis of NDD pathology, the use of a simplified animal model such as *C. elegans* offers a particularly suitable tool for understanding the function of highly conserved disease genes. Indeed, the homology between *C. elegans* and mammalian genomes and the fact that several mutant strains are accessible, makes this system ideal for the identification of complex and conserved molecular pathways. Here we report on a multidisciplinary study by using a *C. elegans* mutant strain collection, available at CNR-IBBR *(BioMemory collection* CNR-IBBR-CELITABASE), aiming to identify mechanistically conserved interactions among conserved NDD genes. In particular, our study is mainly focused on the highly evolutionary conserved *ARX/alr-1* gene, which encodes an homeotic bifunctional transcription factor involved in neuronal differentiation and maturation, whose mutations in human cause multiple NDDs. Using this approach, we are identifying several *ARX/alr-1* target genes implicated in specific neuronal features in nematodes, such as mechano-response and GABAergic neuronal maturation. The identification of these genes will allow to probe the highly conserved history of homeotic transcription factors and their pleiotropic nature underlying the neuronal network architecture.

Keywords: Neurodevelopmental disorders, conserved disease pathways, *ARX*/*alr-1* target genes.

Venue

The meeting will be held in the Art Relais Palazzo Cappuccini, Corso Vittorio Emanuele 730, 80122, Naples, Italy, www.palazzocappuccini.it

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