EMBO
Workshop

III LATIN AMERICAN WORM MEETING

March 15-19
Valparaíso, Chile
2023

Abstracts Book

THIRD LATIN AMERICAN WORM MEETING

The field of biomedical research using *C. elegans* as a model organism has flourished in Latin America in the last decade. This is partly because of a sustained exchange of expertise and tools with the international community through regional meetings and courses. The global *C. elegans* community has made outstanding advances in the last decades, for example in understanding the neural dynamics of living and performing animals or the molecular nature of transgenerational memory of infection and abiotic stresses. Moreover, the nematode has been used as a remarkable biotechnological tool to help find new drugs for animal and plant parasites, and as a sensor for ecotoxicological studies. Our meeting will feature these and other topics that include neuronal regeneration and neuronal diseases, synaptic transmission, whole brain dynamics, epigenetic inheritance, interactions in natural environments among many others. Our previous two meetings, held in Uruguay and Argentina, were successful and instrumental in expanding the networking and training possibilities for students, postdoctoral researchers, and investigators alike. We believe this meeting is an ideal environment to present recent and exciting discoveries using this fantastic nematode.

ORGANIZING COMMITTEE

Andrea Calixto, Centro Interdisciplinario de Neurociencia de Valparaíso, Universidad de Valparaíso, Chile

Andrea Cuentas-Condori, Yale University, USA

María José De Rosa, Instituto de Investigaciones Bioquímicas de Bahía Blanca, Argentina

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Rosa Navarro, Departamento de Biología Celular y Desarrollo, Universidad Nacional Autónoma de México, México

Diego Rayes, Instituto de Investigaciones Bioquímicas de Bahía Blanca, Argentina

Alejandro Vásquez-Rifo, University of Massachusetts Medical School, Worcester, USA

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PROGRAM

DAY 1 MARCH 15th

11:00-15:00 REGISTRATION

15:00-15:15 Introduction to the meeting and the keynote speaker by **Andrea Calixto**

15:15-16:15 **KEYNOTE Piali Sengupta**, Sensational sensory cilia: How cilia shape neuronal responses

Session 1. Chair **Gustavo Salinas**

16:15-16:45 **Javier Apfeld,** Strategic diversity by worms in hydrogen-peroxide survival

16:45-17:00 **Micaela Godoy,** Coupling between transcription and alternative splicing in *C. elegans*

17:00-17:15 **Sebastián Giunti,** Ketogenic modulation of GABAergic signaling in *C. elegans*

17:15-17:30 **Andrea Layedra,** A microfluidic device for simple quantification of chemotaxis with *Caenorhabditis elegans* in neurotoxicological studies

17:30-17:50 COFFEE BREAK

Session 2. Chair **Arantza Barrios**

17:50-18:20 **Judith Yanowitz,** Wombs to Wombs: Lessons in Germline Aging

18:20-18:35 **Enrique Morales-Oliva,** Germ cell fusion and apoptosis is induced by the phosphatidylserine biosynthesis pathway

18:35-18:50 **Rosina Comas-Ghierra,** An incomplete kynurenine pathway supports rhodoquinone but not de novo NAD+ biosynthesis in parasitic worms

18:50-20:30 WELCOME COCKTAIL

DAY 2 MARCH 16th

Session 3. Chair **María Fernanda Hornos**

09:00-09:30 **Monica Colaiacovo,** Regulation of DSB distribution along chromosomes during *C. elegans* meiosis

09:30-09:45 **Julián Valdés,** Behavioral changes induced by starvation and hyperglycemia in *C. elegans*

09:45-10:00 **Albertina Scattolini,** Evaluation of MRSA virulence of structure-based drug against the lipoic acid salvage pathway using *Caenorhabditis elegans*

10:00-10:30 **Christian Braendle,** Natural variation in *C. elegans* egg-laying behaviour modulates an intergenerational fitness trade-off

10:30-10:50 COFFEE BREAK

Session 4. Chair **Marie-Anne Felix**

10:50-11:20 **Natalie Pujol,** How does the skin sense and react to damage?

11:20-11:35 **Bernabé Battista,** A novel conditional unsaturated fatty acids (UFAs) deficient strain in *Caenorhabditis elegans*

11:35-11:50 **Tania Veuthey,** Neural modulation of systemic stress response requires the insulin like-peptide INS-3

11:50-12:20 **Erik Andersen,** Natural variation in anthelmintic resistance

12:20-12:35 **Marcela Brocco,** Neuronal membrane glycoprotein (NGMP-1) is required for stress response in *Caenorhabditis elegans*

12:35-12:50 **Alejandro Vázquez-Rifo,** Genetic and molecular features of P. aeruginosa-induced ribosome cleavage

12:50-13:00 Introduction of the Mentor-Mentee Match Program by Wormboard (**Andrea Calixto**)

13:00-14:30 LUNCH
Lunch with Mentors. Previous matches have been made between mentee and mentor (led by **Alejandro Vazquez and Andrea Cuentas-Condori**)

Session 5. Chair **Andrea Cuentas-Condori**

14:30-15:30 **WORKSHOP** The *C. elegans* Neuronal Gene Expression Map & Network (CeNGEN). **Alexis Weinreb** and **Alec Barrett** (Hammarlund lab, Yale)

15:30-16:00 **Cathy Savage,** *C. elegans* BMP Signaling Regulates Whole Organism Homeostasis

16:00-16:15 **José Antonio Carracedo González,** The paradox of mitochondrial dysfunction and aging: a Boolean approach

16:15-16:30 **Laura Romanelli,** Rhodoquinone as a key molecule for sulfide, cyanide and pathogen response in *C. elegans*

16:30-16:50 COFFEE BREAK

Session 6. Chair **Daiana Silva Avila**

16:50-17:20 **Benjamin Podbilewicz,** Sexual dimorphism of dendritic sculpting in *C. elegans* and its effect on male mating

17:20-17:35 **Florencia Guastaferri,** Exploring age related effects on the lipid metabolism of a *Caenorhabditis elegans* model of Parkinson's disease

17:35-17:50 **Ornella Turani,** Unravelling the physiological role and molecular function of Caenorhabditis elegans betaine-sensitive nicotinic receptors

18:00-20:00 POSTER SESSION I / wine and cheese.

DAY 3 MARCH 17th

Session 7. Chair **Diego de Mendoza**

09:00-09:30 **Ann Rougvie,** The *C. elegans* Genetics Center

09:30-09:45 **Romina D'Almeida,** Neuro-immune responses and transgenerational epigenetic inheritance of *Caenorhabditis elegans* against Candida albicans infection

09:45-10:00 **Paloma Harcha,** The assembly of bacteria living in natural environments shape neuronal integrity and behavioral outputs in *C. elegans*

10:00-10:30 **Alejandro Aballay,** Use of *Caenorhabditis elegans* as a model to study the neural-gut axis

10:30-10:50 COFFEE BREAK

Session 8. Chair **Carolyn Phillips**

10:50-11:35 WORKSHOP **Julián Cerón,** Applications of CRISPR-Cas technologies in *C. elegans*

11:35-11:50 **Eugenia Carla Kuhn,** Monthly ecotoxicological assessment of medium Uruguay river - Brazil using *Caenorhabditis elegans* as a biomonitor

11:50-12:05 **Rosa Navarro,** The RNA binding protein GLA-3 is important to protect germ cells from stress

12:10-13:00 NETWORKING Speed dates. Chairs **Daniel Hochbaum and Rosa Navarro**

13:00-14:30 LUNCH

14:30-15:30 DISCUSSION WOMEN IN SCIENCE. Presented by a panel of young and established investigators with the participation of the audience

Session 9. Chair **Eleni Gourgou**

15:30-16:00 **Carolyn Phillips,** HRDE-2 regulates small RNA specificity for the nuclear Argonaute protein HRDE-1

16:00-16:15 **Roberto Carlos Martínez Padilla,** Mathematical modeling of microRNA-transcription factor networks in *Caenorhabditis elegans* exposed to high-glucose diets

16:15-16:45 **Luisa Cochella**, Quantitative control of morphogenesis by a deeply conserved miRNA family

16:45-17:15 COFFEE BREAK

17:15-18:00 Virtual lecture **Daniel Colon Ramos,** Structural and developmental principles of neuropil assembly in *C. elegans* (Introduction by **Diego Rayes**)

18:00- 20:00 POSTER SESSION II / wine and cheese.

DAY 4 MARCH 18th

Session 10. Chair **Marcela Brocco**

09:00-10:40 **IBRO SYMPOSIUM** Topics in neuroscience: from neurodevelopment to neurodegeneration

09:00-09:30 **Eleni Gourgou,** Multisensory learning in engineered microenvironments

09:30-09:45 **Diego Becerra,** Can we know what it is like to be a worm? Integrated information and high order interdependences in *C. elegans*'s sleep-wake dynamics

09:45-10:00 **María Gabriela Blanco,** Behavioral State Transitions in *Caenorhabditis elegans*

10:00-10:30 **Arantza Barrios,** Switching odour preferences through experience

10:30-10:50 COFFEE BREAK

Session 11. Chair **Judith Yanowitz**

10:50-11:05 **Margaret A. Titus** MyTH-FERM Myosins in the *C. elegans* Intestine

11:05- 12:00 Flash Talks from posters.

Free afternoon

20:00 SOCIAL EVENT PARTY

DAY 5 MARCH 19th

Session 12. Chair **Luisa Cochella**

09:00-09:30 **Marie-Anne Félix,** Natural variation in C. elegans: vulva development and epigenetic heredity

09:30-09:45 **Francisco Silva,** Born to be a wild worm: differential circadian rhythms between domesticated N2 and wild Caenorhabditis elegans isolates

09:45-10:00 **Andrea Cuentas-Condori,** Synapse organization and function of dual-transmitter neurons.

10:00-10:15 **Cecilia Vranych,** Cannabinoids activate the insulin pathway to modulate mobilization of cholesterol in Caenorhabditis elegans

10:15-10:35 COFFEE BREAK

10:35-11:35 **CLOSING LECTURE David Gems,** What is aging? Lessons from C. elegans. Introduction by **Rosa Navarro**

11:40-12:00 POSTER PRIZES (Led by **María José de Rosa**) AND CLOSING REMARKS (**Organization of the Meeting**)

ABOUT VALPARAÍSO

Third Latin American Worm Meeting will be held from March 15th to the 19th in Valparaíso, a city that faces the Pacific Ocean in central Chile. While over a million people live in the neighboring cities, Valparaíso itself has about 300,000 inhabitants, making it easy for people to walk and use public transportation. The historic quarter of Valparaiso is a UNESCO World Heritage Site. The hills Cerro Alegre and Cerro Concepción are at the heart of its historic quarter and are an important tourist attraction due to its many bars, pubs, restaurants, and hotels. The fifteen urban elevators -a heritage from the industrial revolution- and the trolleybuses (the oldest in the world still in operation) are two unique characteristics of the city.

Valparaíso is just one and a half hours from Santiago's International Airport and the city of Santiago. From this airport, connections are possible to the major tourist attractions in the country, including Patagonia (Torres del Paine), the Atacama Desert (San Pedro de Atacama), and Rapa Nui (Easter Island).

The Meeting will take place at the Valparaíso Cultural Park. The Cultural Park is a public space of 1.5 ha (3.7 ac) recently built on the site of Valparaíso's former jail. It includes an auditorium with a capacity of around 300 seats, where all talks will be held. The Cultural Park is a ten-minute bus ride and a 10-30-minute walk from most Valparaíso hotels.

THE VENUE
PARQUE CULTURAL DE VALPARAÍSO (CULTURAL PARK OF VALPARAÍSO)

The Symposium will take place at the Parque Cultural de Valparaíso (PCdV). It is located in Cerro Cárcel, which was the prison of Valparíso until 1994. Today it serves the community as a Cultural Park.

Address: Calle Cárcel 471, Cerro Cárcel, Valparaíso.

www.parquecultural.cl

PALACIO BABURIZZA

The final Social Event will be held in the Baburizza Palace.

This historic site is an Art Deco and Art Nouveau building built in 1916 and is located at the Paseo Yugoslavo. Since 1971 it has been the Fine Arts Museum of Valparaiso. It was declared a National Monument in 1979.

Address: Paseo Yugoslavo 176, Cerro Alegre,Valparaíso

A BRIEF HISTORY OF THE LATIN AMERICAN *C. ELEGANS* COMMUNITY

Research using *C. elegans* began in Latin America 20 years ago. Many Latin American student and postdocs that trained in *C. elegans* laboratories in the northern hemisphere, returned home during the 2000s and started their own labs. In 2011 a few pioneers organized the first Symposia on *C. elegans* in the University of Quilmes in Argentina. They invited other firsts from Chile, Uruguay and Brazil. In 2017, a team from the Pasteur Institute in Montevideo Uruguay, organized the first Latin American Worm Meeting (LAWM), with the participation of Nobel Prize laureate Martin Chalfie (Chemistry, for the discovery and use of the Green Fluorescent Protein) and more than 15 international speakers and students and researchers from Chile, Argentina, Uruguay, Brazil, Mexico and Colombia for a very successful meeting of almost 100 people. The second LAWN took place in 2020, in Rosario Argentina, with similar number of international speakers and more presence of local scientists and students. Lasker Award Laureate Victor Ambros (discovery of the first microRNA) delivered the keynote and Marian Walhout (bacterial impact on host life history traits and response to drugs), gave the closing lecture. Moving from the Atlantic to the Pacific, the meeting will take place this year in the beautiful and patrimonial city of Valparaiso, Chile. This meeting has the largest number of participants thus far and is honored to open with the Keynote of Piali Sengupta (Molecular mechanisms of environmental perception). The closing lecture will be given by David Gems (the complexities of ageing). Thanks to the support from EMBO and ICGEB our meeting is accessible to Latin American scientists historically disenfranchised from participation in global meetings, and has the clear intention of bringing excellent unpublished science to the Southern Hemisphere.

CENTRO INTERDISCIPLINARIO DE NEUROCIENCIA DE VALPARAÍSO

The CINV, located at the University of Valparaiso is a research institute, home of one of the first and still one of the few worm labs in Chile. The CINV has been recognized by the university and the Ministry of Science as a center of excellence and believes such excellence can only be achieved by integrating knowledge coming from all forms of life. The center purposefully included the pioneer organism *C. elegans* in recognition of its power in the study of neuroscience and science in general. The center is extremely proud to host the Third Latin American *C. elegans* meeting and to receive the worm community in our beloved city. The CINV (www.cinv.cl) is dedicated to understanding how the nervous system senses its surrounding and includes biophysicists, physiologists, neurobiologist and experts in bioinformatics and molecular modeling. Its scope of study spans from the inner workings of proteins transducing signals from the outside world to animal behavior.

ABSTRACTS

KEYNOTE LECTURE

Sensational sensory cilia: How cilia shape neuronal responses

Piali Sengupta
Department of Biology, Brandeis University, Waltham, MA, USA

Sensory neurons contain structurally diverse cilia that house signal transduction molecules and play essential roles in olfaction, hearing, and photoreception. Complex cilia morphologies dictate the concentration and organization of signaling molecules within them, and are thus considered critical for precisely shaping sensory responses. However, the contribution of unique cilia morphologies to sensory signaling is poorly understood. Chemosensory neurons in *C. elegans* are specialized to respond to unique subsets of chemical and other stimuli and exhibit a range of morphologically distinct cilia. These organelles are built by the process of intraflagellar transport (IFT) which traffics structural and signaling components into and out of cilia. Mutations in IFT genes result in severe cilia structural defects. Using genetics, in vivo calcium imaging, and high-resolution behavioral assays, we find that IFT and cilia morphologies differentially contribute to individual sensory neuron responses and chemosensory behaviors. A minimum cilium length but not IFT regulates chemosensory responses in a subset of neurons, whereas cilia morphology and IFT differentially regulate olfactory response dynamics in neurons with complex cilia. Our work describes how specialized cilia morphologies contribute to the unique responses of individual chemosensory neurons in *C. elegans*, and highlights the importance of these structures in precisely shaping sensory behaviors.

CLOSING LECTURE

What is aging? Lessons from *C. elegans*

David Gems
Institute of Healthy Ageing, and Department of Genetics, Evolution and Environment, University College London, London, UK

Although aging is the greatest cause of disease worldwide, its underlying causes are still poorly understood. The discovery in the 1980s of *C. elegans* mutants with greatly extended lifespan was really exciting. Not only did it imply the existence of core mechanisms of aging as a whole, but also their presence in a highly tractable model organism suggested that the study of *C. elegans* could soon reveal the secrets of aging. Entering the field in 1993, I guessed that this would take 5-10 years at most. It was soon established by the Ruvkun and Kenyon labs that insulin/IGF-1 signaling (IIS) is a major regulator of aging, acting in particular via the FoxO transcription factor DAF-16. But identifying the aging process that DAF-16 controls has proven to be expectedly difficult.

My talk will present the results of attempts by my group to get beyond the DAF-16 roadblock, to discover what aging in *C. elegans* is in a fundamental sense. This involves a number of new approaches, questions and ideas, including: How does IIS cause age-related diseases, and how do these cause death? Are the same pathophysiological principles operative in the development of age-related diseases in *C. elegans* and mammals? Does IIS shorten lifespan by promoting futile programmatic mechanisms as proposed by recent theory, rather than through effects on molecular damage and somatic maintenance? Does IIS promote semelparous reproductive death in *C. elegans*, similar to that seen in Pacific salmon? And: could earlier death in post-reproductive *C. elegans* have evolved to promote inclusive fitness?

PRESENTATIONS

Use of *Caenorhabditis elegans* as a model to study the neural-gut axis

Alejandro Aballay
Oregon Health & Science University, USA

Animals have evolved sophisticated mechanisms to modify specific properties in response to changes such as those that occur during the response to microbial infections. The nervous system, which can sense many types of environmental stimuli, may help integrate information to activate behavioral and molecular immune defenses. This general control of immune pathways is crucial for the homeostasis of the organisms because the activation of the immune system accounts for the major physiological, metabolic, and pathological responses to infections. We found that G-protein coupled receptor signaling in specific sensory neurons in the nervous system of *Caenorhabditis elegans* appears to control behavioral response to pathogens, microbial-killing pathways, and stress-induced pathways that play a key role in cellular homeostasis during responses against bacterial infections. The mechanisms by which modulation of neuroendocrine pathways provide feedback from the intestine during infection to modulate the behavior, learning, and microbial perception by the host will be presented.

Natural variation in anthelmintic resistance

Erik Andersen
Northwestern University, USA

Parasitic nematodes infect over one billion people worldwide, especially in developing countries. Anti-nematode drugs or anthelmintics are our only method to control this massive burden on the educational attainment and health of these people. Because of overuse, anthelmintic resistance is rising rapidly in human parasites and omnipresent in veterinary parasitic nematodes. Using free-living nematode species, like *C. elegans*, my lab investigates natural sources of anthelmintic resistance to identify and then exploit these mechanisms for parasite control. I will present our progress performing unbiased genome-wide association studies to discover resistance loci across many anthelmintics, including novel mechanisms of emodepside, Cry5B, and thiabendazole resistance. We also are working to create new model parasitic nematode systems to investigate anthelmintic resistance in worms distantly related to Caenorhabditis species. We have created new genomes, established genetic crossing schemes, and investigated resistance loci.

Strategic diversity by worms in hydrogen-peroxide survival

Javier Apfeld
Northeastern University, USA

In my lab we are trying to figure out the strategies that *C. elegans* worms use to deal with the damaging effects of hydrogen peroxide—the preeminent chemical weapon that organisms use for combat. Bacteria, fungi, plants, and animals have long been known to excrete large quantities of hydrogen peroxide (H_2O_2) to attack their prey and pathogens. H_2O_2 is also a byproduct of aerobic respiration. How do worms deal with the lethal threat of H_2O_2? I will be talking about three different types of strategies that worms use to decide when to induce behavioral and cellular H_2O_2 defenses in response to environmental information. One involves escaping lethal levels of H_2O_2, another involves guessing when self-defense is not needed, and yet another involves preemptively inducing defenses when an inherent enhancer of the reactivity of H_2O_2 is detected. We think that by relying on a combination of strategies, *C. elegans* can better manage the challenge of avoiding inducing costly H_2O_2 defenses that can cause undesirable side effects at inappropriate times.

The *C. elegans* Neuronal Gene Expression Map & Network CeNGEN
A CeNGEN Primer: Getting the most from a neuron-specific gene expression reference

Alec Barrett and Alexis Weinreb
Hammarlund lab, Yale University, USA

The CeNGEN consortium (*C. elegans* Neuronal Gene Expression Map Network) has produced a comprehensive description of gene expression for the entire *C. elegans* nervous system that includes. single-cell RNA-seq profiles of 128 neuron types [1]. We are also using FACS to isolate individual neuron types for “bulk” or whole transcriptome sequencing to detect noncoding RNAs and alternative splicing events [2]. This workshop will provide a practical guide for exploiting CeNGEN RNA-Seq datasets, along with an overview of techniques for generating and analyzing RNA-Seq data in *C. elegans*. We will describe our experimental methods for generating these datasets, including how to dissociate worms into a single cell suspension, how to isolate *C. elegans* neurons by FACS, how to perform 10x Genomics single-cell RNA-Seq, and how to obtain high-quality data from low-input bulk RNA-Seq. We will discuss 1) Novel approaches to detecting gene expression events; 2) A “clean-up” computational method that removes non-target counts from bulk samples; 3) Integration of bulk and single-cell datasets; 4) Quantification of alternative splicing across the nervous system. CeNGEN has created publicly available web applications for detailed descriptions of cell type-specific usage of protein coding genes, noncoding RNAs, and splice variants. The dataset underlying each web app is downloadable. We will introduce these tools and demonstrate how to use them to empower your research projects.

Switching odour preferences through experience

Arantza Barrios
Department of Cell and Developmental Biology, University College London, UK

Punishing and rewarding experiences can change the valence of sensory stimuli and condition animal behaviour in opposite directions, resulting in avoidance or approach. Often, however, stimuli are encountered with both positive and negative experiences. How is such conflicting information represented in the brain and resolved into a behavioural decision? We address this question by dissecting a circuit for sexual conditioning in *C. elegans*. Sexual conditioning is a learning paradigm in which an odour is conditioned with both a punishment (starvation) and a reward (mates) and that results in odour approach. We find that positive and negative experiences are both encoded by PDF neuropeptide signaling acting on and being released from different neurons. Each experience creates a separate memory or engram in the circuit for odour processing. This results in the sensorimotor representation of odour being different in naïve and sexually conditioned animals despite both displaying approach. Our results reveal that positive valence can be flexibly represented according to stimulus prediction.

Natural variation in *C. elegans* egg-laying behaviour modulates an intergenerational fitness trade-off

Christian Braendle
Université Côte d'Azur, CNRS, Inserm, IBV, Nice, France

Evolutionary transitions from oviparity to viviparity are frequent across diverse taxa and many species also display intraspecific variation in egg retention, that is, an intermediate type of parity by laying eggs containing embryos at advanced stages of development. How such natural quantitative variation in egg retention arises through differences in genetics, behaviour and physiology – and how this variation ultimately connects to variation in specific fitness components – is not well-understood. Here we focus on intraspecific variation in constitutive retention of fertilized eggs and internal hatching of the nematode *Caenorhabditis elegans*. Analysing a panel of ~400 wild strains, we report highly variable intra-uterine retention of fertilized eggs, with a fraction of strains showed either strongly reduced or increased egg retention. We provide evidence for multiple evolutionary origins of such phenotypic extremes and identify candidate QTL (Quantitative Trait Loci) explaining natural variation in egg retention. Characterizing a subset of wild strains, we show that natural variation in egg-laying behaviour contributes to observed divergence in egg retention. Changes in egg-laying behaviour in response to pharmacological treatments and controlled genetic manipulation of endogenous serotonin signalling were strongly dependent on genetic background, indicative of natural variation in neuromodulatory architecture of the egg-laying circuit. These results suggest that *C. elegans* neural circuit activity can readily evolve to alter egg-laying behaviour, ultimately resulting in variable duration of embryogenesis in utero. Examining potential costs and benefits of natural variation in *C. elegans* egg laying, we show that high egg retention can reduce maternal fertility and survival due to frequent internal larval hatching. In contrast, genotypes with high egg retention may benefit from improved offspring protection against environmental insults and a competitive advantage as offspring exhibit a shortened extra-uterine developmental time to reproductive maturity. Observed natural variation in *C. elegans* egg laying may therefore modulate an intergenerational trade-off between alternative fitness components.

Applications of CRISPR-Cas technologies in *C. elegans*

Julián Cerón
Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet de Llobregat, Barcelona, Spain

Genome editing with CRISPR-Cas9 is being a game-changer tool in biological research. Although many of the optimizations are orientated toward clinical applications, the uses of CRISPR-Cas in model organisms are also evolving fast. In this context, our favorite animal models have several advantages as the short life cycle, the germline syncytium, and its hermaphroditism that allow us to efficiently test new conditions and applications in a short period of time. I'll summarize the methods to make endogenous gene reporters and comment on the benefits of humanizing *C. elegans* genes for biomedical research. Finally, I'll show some examples of how are we exploiting *C. elegans* to explore the potential of new Cas nucleases and to model human genetic diseases.

Quantitative control of morphogenesis by a deeply conserved miRNA family

Luisa Cochella
Johns Hopkins University, USA

MicroRNAs are essential for embryonic development. In most studied animals, the essential miRNAs during embryogenesis form miRNA families with multiple members. In *C. elegans,* embryonic arrest is caused primarily by loss of two miRNA families, both highly expressed in the embryo: the miR-35 and miR-51 families. Here, we set out to investigate the function of miR-51, which is evolutionarily related to miR-100, present from the base of Eumetazoa. Simultaneous deletion of the six members of this family leads to failed morphogenesis. However, the contributions of the different family members to larval development differ and it is unclear whether this is due to their differences in sequence, expression pattern or dose. Moreover, despite the importance of this miRNA family, we do not know its functionally relevant targets and how they affect morphogenesis. We have found that sequence differences do not account for the distinct contributions of the miR-51 family members, and rather they regulate a common target or set of targets in a dose-dependent manner. Using target prediction and conservation analysis, followed by RNA-seq and analysis of endogenous reporters, we find that miR-51 is a direct repressor components of the extracellular matrix. We are currently exploring the functional consequences of their deregulation. Remarkably, some of the validated targets in *C. elegans* are also predicted targets in zebrafish, mice and humans, suggesting a possibly conserved function for the most ancient animal miRNA.

Regulation of DSB distribution along chromosomes during *C. elegans* meiosis

Monica Colaiacovo
Department of Genetics, Harvard Medical School, USA

Errors in achieving accurate chromosome segregation during meiosis lead to the formation of eggs and sperm carrying an incorrect number of chromosomes which can result in miscarriages, stillbirths, and congenital abnormalities. The formation of programmed DNA double-strand breaks (DSBs) and the repair of a subset of these DSBs via crossover formation are tightly regulated events that ensure accurate chromosome segregation during meiosis. Studies in various species have shown that meiotic DSBs are not randomly distributed throughout the genome but tend to preferentially form at DSB hotspots. Recent studies in *C. elegans* have revealed that meiotic DSBs are also not evenly distributed along its holocentric chromosomes and instead are enriched at the terminal thirds of chromosomes. These are also the domains in which crossover recombination events are more prevalent in this organism. How this positional regulation is implemented remains poorly understood. Here, using: 1) the spatiotemporal resolution of meiotic stages within the *C. elegans* germline and high-resolution imaging of computationally-straightened chromosomes immunostained for the recombinase RAD-51, and 2) an inducible Mos1-based DSB system coupled with ChIP-qPCR analysis, we investigated the contribution of different factors to the regulation of meiotic DSB distribution. These findings will be discussed and presented in the context of how DSB distribution and subsequent crossover position are tightly regulated to ensure proper late prophase I chromosome remodeling and accurate chromosome segregation in *C. elegans*.

Structural and developmental principles of neuropil assembly in *C. elegans*

Daniel Colon-Ramos
Department of Cell Biology and Neuroscience, Yale University, USA

Neuropil is a fundamental form of tissue organization within the brain, in which densely packed neurons synaptically interconnect into precise circuit architecture. However, the structural and developmental principles that govern this nanoscale precision remain largely unknown. Here we use an iterative data coarse-graining algorithm termed ‘diffusion condensation’ to identify nested circuit structures within the *Caenorhabditis elegans* neuropil, which is known as the nerve ring. We show that the nerve ring neuropil is largely organized into four strata that are composed of related behavioral circuits. The stratified architecture of the neuropil is a geometrical representation of the functional segregation of sensory information and motor outputs, with specific sensory organs and muscle quadrants mapping onto particular neuropil strata. We identify groups of neurons with unique morphologies that integrate information across strata and that create neural structures that cage the strata within the nerve ring. We use high resolution light-sheet microscopy coupled with lineage-tracing and cell-tracking algorithms to resolve the developmental sequence and reveal principles of cell position, migration and outgrowth that guide stratified neuropil organization. Our results uncover conserved structural design principles that underlie the architecture and function of the nerve ring neuropil, and reveal a temporal progression of outgrowth—based on pioneer neurons—that guides the hierarchical development of the layered neuropil. Our findings provide a systematic blueprint for using structural and developmental approaches to understand neuropil organization within the brain.

Natural variation in *C. elegans*: vulva development and epigenetic heredity

Marie-Anne Félix
Université Paris, France

We use the nematode *C. elegans* to answer evolutionary questions, making use of the knowledge of molecular, cell, developmental and physiological processes in this model animal. As a resource, we have collected *Caenorhabditis* species and its natural associates and pathogens. A key evolutionary question is the extent to which the process of phenotype construction (e.g. development) biases and constrains phenotypic evolution. In other words, do directions of phenotypic space with high sensitivity to random mutation correspond to directions of fast evolution? The development of the *C. elegans* vulva provides a model system where the fates and variational properties of each of six precursor cells can be compared quantitatively. *Caenorhabditis* and *Oscheius* are two genera with contrasted patterns of evolutionary variation in these cell fates. We examined the sensitivity of the fates of the six cells to random mutation and their evolutionary variation within and among species of each genus. Overall, our results indicate that the sensitivity to molecular dose variation of a developmental system may produce evolutionary trends at the phenotypic level. The recent molecular insights into non-standard heredity (epigenetic heredity) raise evolutionary questions. In *C. elegans,* non-standard genetic heredity includes the transmission of small RNAs affecting histone modifications. Our work shows that *C. elegans* harbors natural genetic variation in such non-genetic inheritance phenomena, affecting for instance the duration of the memory across generations.

Multisensory learning in engineered microenvironments

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The mechanisms of learning and memory are central topics in contemporary neurobiology. Despite its only 302 neurons, *C. elegans* demonstrates remarkable associative and non-associative learning, studied mainly in the context of chemical cues. Surprisingly, spatial learning in nematodes had not been explored until recently, mainly due to the lack of appropriate experimental platforms. We pioneered that area, as we designed a nematode-friendly maze arena, and developed a behavioral assay that allows for the assessment of spatial learning in nematodes, for the first time. We showed *that C. elegans* young adults locate food in T-shaped mazes and based on this experience, learn to reach a specific side maze arm in a similar but empty maze. Learning depends on mechanosensation and proprioception. We found that dietary and behavioral interventions can delay aging-driven decline of maze learning in middle-aged nematodes. In parallel, we are developing a mathematical framework that captures the dynamics of the steering circuitry, predicts the role of key neuronal components, and generates new testable hypotheses. To create more realistic terrains, we have developed a prototype 3D printer, that uses nematode-friendly hydrogel as ink, and prints 3D behavioral arenas. We aspire to characterize *C. elegans* 3D behavior, and to suggest translatable interventions that protect against aging-related decline of cognitive-like functions.

HRDE-2 regulates small RNA specificity for the nuclear Argonaute protein HRDE-1

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RNA silencing is a critically important mechanism through which cells regulate gene expression and protect the genome against aberrant RNAs, transposons, and viruses. RNA silencing is mediated by small non-coding RNAs, which are bound by Argonaute proteins and regulate complementary mRNAs at the level of transcription, translation, and RNA stability.

The goal of my lab is to understand how small RNAs function and with what proteins they interact to exert their regulatory activity. Specifically, since there are multiple Argonaute proteins and different classes of small regulatory RNAs, a major focus of our work has been to determine how each Argonaute protein recognizes and binds the correct small regulatory RNAs. One protein-of-interest has been HRDE-2, which we have discovered regulates localization and small RNA binding for the nuclear Argonaute protein HRDE-1. First, we found that when HRDE-1 cannot bind its preferred small RNAs, it accumulates in germ granules, and this germ granule localization is dependent on HRDE-2. Second, we found that in the absence of HRDE-2, HRDE-1 binds exclusively to an incorrect class of small RNAs. Thus, our work demonstrates that HRDE-2 is critical to ensure correct small RNAs are used to guide nuclear RNA silencing in the *C. elegans* germline.

Sexual dimorphism of dendritic sculpting in *C. elegans* and its effect on male mating

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Dendritic arbors show extreme variability between species and neuron type, yet it is often unclear whether and how these variations contribute to a neuron's function. Using the stereotypic branched structure of the *C. elegans* PVD polymodal neuron, we characterize a sexually dimorphic branching pattern which influences some sex-specific behaviors.

How does the skin sense and react to damage?

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All multicellular organisms must protect themselves from injury and pathogens. Lacking an adaptive immune system or motile immune cells, *C. elegans* relies on its epithelial barrier to defend against environmental threats. This makes it a powerful model to address the question of how epithelial cells detect damage. In *C. elegans*, the skin is characterized by a rigid but flexible aECM, the cuticle, that surrounds the epidermal syncytium. We have shown that changes in the structure of the aECM can mimic physical injury and natural fungal infection, and activate an immune response characterized by the induction of antimicrobial peptides in the epidermis. Tissue repair is related to this innate response, and involves myosin-independent actin ring closure guided by the microtubule-tip protein EB1. This intimate relationship between aECM integrity and the epidermal cytoskeleton is also observed during molting. Indeed, like the cell wall of plants or yeast, the nematode aECM provides the mechanical support that is provided by the cortical actin meshwork in most animal cells. Thus, in the adult worm, the epidermal cytoskeleton is disorganized, in contrast to the last molt when it is highly structured. Furthermore, during molting, the immune response is induced, potentially as a prophylactic protective mechanism. We therefore hypothesize that any change in aECM tension, due to damage or molting, will induce coordinated cytoskeletal rearrangements and an immune response in the epidermis. We are now exploring the biophysical properties of the skin to understand the mechanical coupling of the aECM to the epidermis.

Caenorhabditis Genetics Center (CGC): The Latin American Perspective

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The Caenorhabditis Genetics Center (CGC) promotes *C. elegans* research by curating important, genetically characterized nematode stocks and distributing them upon request to researchers and science educators throughout the world. The CGC is housed at the University of Minnesota and is supported by the National Institutes of Health - Office of Research Infrastructure Programs (NIH-ORIP) and nominal user fees. We strive to have at least one allele of every published gene and all useful chromosome rearrangements, duplications and deficiencies. Our catalog of more than 24,500 different strains also includes selected multiple-mutant stocks, tagged endogenous loci, and genetic tool strains for various applications such as inducible gene expression. In addition to curating and distributing strains, the CGC carries out small research projects to enhance the genetic tool-kit available to *C. elegans* researchers.
These projects have included the labeling of existing balancer chromosomes with fluorescent markers and deleting or tagging miRNA loci. An additional NIH-funded project (collaborative with the Sternberg and Hutter labs) aims to knockout *C. elegans* genes that are conserved to humans, with one focus on genes associated with Alzheimer´s disease. Each of these projects will prioritize genes (or balancers) for targeting upon user request. A CGC status report will be presented, with a focus on our Latin American user base. A discussion will be held to obtain feedback and exchange ideas about how we can better serve the research community.

C. elegans BMP Signaling Regulates Whole Organism Homeostasis

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Bone morphogenetic proteins (BMPs) are conserved members of the Transforming Growth Factor-β (TGF-β) family of secreted signaling ligands. BMPs are well known for their roles in development, but are emerging as regulators of homeostasis. We are investigating how this signaling pathway regulates two homeostatic functions: lipid metabolism and response to bacterial pathogens. We demonstrated that DBL-1/BMP is required for normal fat accumulation and that it does so in part by downregulation of insulin/IGF-1-like signaling through the DAF-2 insulin-like receptor. The DBL-1 pathway acts nonautonomously on intestinal fat accumulation by regulating *ins-4* expression in the hypodermis. Furthermore, loss of *dbl-1/BMP* increases the responsiveness of DAF16/FoxO and decreases the responsiveness of SKN-1/Nrf to DAF-2 signaling at the level of nuclear localization. DBL-1/BMP, via its signaling pathway including the transcription factor SMA-3/Smad, has been shown by others to regulate innate immune response. We have now determined that SMA-3/Smad also acts nonautonomously in the pharynx and the hypodermis to regulate survival on pathogen. It does so in part by regulation of antimicrobial peptides and of pharyngeal pumping. Interestingly, we have shown that exposure to bacterial pathogens leads to DBL-1/BMP-dependent mobilization of fat stores that may connect these two functions. Finally, we find unexpected crosstalk between BMP and TGFβ/Activin family members in the immune response. This cooperation may allow differentiation of the acute response to pathogens from ubiquitous signaling functions.

Wombs to Wombs: Lessons in Germline Aging

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More than one in ten couples world-wide have trouble conceiving. This is a dramatic increase from half a century ago and at least partially reflects many couples' decisions to start their families at older ages. Unfortunately, in both women and men, age decreases gamete quality. In part this age effect is due to the decline in stability of factors that hold chromosomes together on the meiotic spindle; in part, it is due to inherently unfavorable crossover configurations that arise during meiosis as the maternal and paternal chromosomes experience genetic exchange. We are interested in understanding how age impacts meiotic processes and vice versa. I will address the effects of age on multiple steps of crossover formation, how transgenerational mutations can be further perturbed by maternal age, and the recent finding that mutations in meiotic genes have a profound effect on the systemic aging program.

SELECTED ABSTRACTS

A novel conditional unsaturated fatty acids (UFAs) deficient strain in *Caenorhabditis elegans*

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Lipids perform a wide variety of functions in the cell, from optimal membrane fluidity to energy homeostasis as a result of their highly reduced state. Although all living organisms must produce thousands of distinct lipids, a unique aspect of *Caenorhabditis elegans* metabolism is the ability to synthesize a wide range of polyunsaturated fatty acids (PUFAs). The pathway for unsaturated fatty acids (UFAs) synthesis in *C. elegans* begins with the desaturation of palmitic acid (16:0) to palmitoleic acid (16:1) or the elongation of 16:0 to stearic acid (18:0). The last one is further desaturated to oleic acid (18:1), that in the nematode is further used to form all the PUFAs. The biosynthesis of 16:1 and 18:1 requires three Δ9 desaturases named FAT-5, FAT-6 and FAT-7. Given the essentiality of UFAs, the *fat-5;fat-6;fat-7* triple mutant strain is lethal. Thus, using CRISPR-Cas9 technology we have constructed a conditional *fat-7* mutant in a *fat-5;fat-6* background . This strain allows the inducible suppression of FAT-7 activity in living worms. We have characterized the phenotypic consequences of total UFAs deficiency in nematode's growth and fertility. We have found that UFA seems to be crucial for L2-L3 molting. Furthermore, this strain is a novel tool to study a plethora of processes involving the complete conditional depletion of UFAs in the context of a whole animal.

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Can we know what it is like to be a worm? Integrated information and high order interdependences in *C. elegans*'s sleep-wake dynamics

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Sleep is ubiquitous within Metazoa, but consciousness is traditionally attributed to few animal lineages. *Caenorhabditis elegans*, displays spontaneous bouts of locomotor quiescence and developmentally-timed, stress-induced, and hypoxia-induced quiescence. These quiescent states are regarded as true sleep. Given the relationship between sleep and consciousness shifts, measuring dynamic variations in neural activity during sleep-wake dynamics is a promising paradigm to assess consciousness in distant branches of the phylogenetic tree. Here, using requested data from Nichols et al. (2017), different informational metrics were implemented in a hypoxia-induced quiescence experiment with *npr-1 C. elegans* mutants expressing a genetically encoded calcium-sensor (NLS-GCaMP5K) that allows the recording of calcium dynamics from several individual neurons. Their functional connectivity was characterized using graph topological metrics, as well as high-order interdependences to unveil synergistic and redundant interactions.
S-information, which measures the total high-order interaction among three or more time series, enabled us to distinguish sleep from wakefulness. By looking at the n-plets of neurons that maximize S-information values as the order of interaction increases, we found that the system is redundancy-dominated, and the increase in redundancy is steeper when awake. The 24-plets of neurons with the highest values in synergy and S-information, partially overlap with a previously documented motor circuit crucial for the induction of sleep. Applying informational metrics, i.e. a proxy of the Integrated Information Theory of consciousness' Phi, we obtained negative values during both sleep and wakefulness. This can be preliminarily interpreted as absence of phenomenal consciousness, but alternative approaches to infer consciousness must be discussed.

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Behavioral State Transitions in *Caenorhabditis elegans*

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Changes in food seeking behaviors are influenced by physiological internal states. During foraging, animals can switch from one state to another, for example, from satiety while feeding to hunger and stress when there is food shortage. Referred to as the “happiness hormone”, serotonin has been related in many animals to modulate feeding in favorable environmental conditions. On the other hand, noradrenaline is the major conserved neurotransmitter implicated in triggering a stress response. In this work, we are interested in how these neurotransmitters interact to modulate the animal`s internal state in behavioral transitions. The complexity of the mammalian brain complicates the study of neuronal processes. The nematode *Caenorhabditis elegans* is suitable for understanding neuronal signaling because of its simple and well-described nervous system. During a prolonged fasting period, animals decrease their locomotion. We demonstrate that locomotion can be resumed by adding tyramine, the analog of noradrenaline in invertebrates. Interestingly, serotonin produces the opposite effect by reducing locomotion. These results suggest that serotonin acts antagonistically to tyramine. Also, when the environment improves and fasted animals encounter food, they release serotonin to slow their locomotion and promote feeding. We found that this slowing response and the activity of the serotonergic neurons upon food encounter are enhanced in tyramine-deficient mutants. Given that tyramine levels decrease during fasting, we hypothesize that the lack of tyramine upon fasting disinhibits the serotonergic neurons and favors their activity upon refeeding. Considering the conservation of neuronal components, we believe that our results may contribute to the understanding of the nervous control of state dependent foraging strategies.

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The paradox of mitochondrial dysfunction and aging: a boolean approach

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The use of systems biology to understand complex processes is a powerful tool, and one of the more complex processes to studying using these tools is aging. The study of long-lived mutants in *C. elegans* has generated much data about molecular and cellular interactions. One of these well-studied mutants is *clk-1* which encodes for a ubiquitin precursor and has shown an interesting pleiotropic phenotype during aging. There are characteristic changes such as slow rate behaviors, high levels of mitochondrial ROS, induction of autophagy, and changes in metabolism. However, the complex relationship between these molecular changes and the phenotype (in neuromuscular behaviors and lifespan extension) must be clarified. We first replicated and then analyzed these interactions in this work through a novel boolean network, and then we deduced the differential equations for each node from the boolean rules. We have seen that *aak-2* is a critical gene for the long lifespan induction of *clk-1* because of its mediation in multiple processes and its changes in the network attractors, as well as lower rates in neuromuscular behaviors, if this gene is deleted either in the network or the double mutant (*clk-1;aak-2*). We also found a cyclic attractor (explained by the loop of the interactions between ROS, *aak-2*, and *hif-1* in the network) and a static attractor from the continuous model.

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An incomplete kynurenine pathway supports rhodoquinone but not de novo NAD+ biosynthesis in parasitic worms

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Background and aims. ATP and NAD^+ are the energy and redox currencies of life. Under the hypoxic conditions found in the gastrointestinal tract of their hosts, helminths obtain ATP using an alternative electron transport chain in which NADH serves as electron donor and rhodoquinone (RQ) as electron transporter. The kynurenine pathway, which is the main tryptophan catabolic route, generates the precursors for RQ and *de novo* NAD^+ biosynthesis. Our aim was to address RQ and NAD^+ biosynthesis in helminths, which have not been thoroughly studied despite their biochemical and potential pharmacological relevance. **Methods.** Sequence analysis of helminths genomes for all the genes involved in RQ and NAD^+ biosynthesis was performed. In-silico derived hypotheses were then experimentally addressed by HPLC-MS target metabolomics. **Results**. Of the kynurenine pathway genes, only the kynureninase and tryptophan/indoleamine dioxygenases are encoded by all helminths. Metabolomic analysis in *C. elegans* mutant strains and species lacking the other genes of the pathway revealed that their absence does not preclude RQ biosynthesis. In addition, we found that most helminths were unable to synthesize NAD^+ *de novo*, relying exclusively on rescue

pathways. In line with their streamlined genomes, cestodes are exclusively reliant on nicotinamide for NAD^+ synthesis. Indeed, the inhibition of the NAD^+ recycling enzyme nicotinamide phosphoribosyltransferase led to parasite death after 7-days incubation. **Conclusions.** Our results demonstrate that an incomplete kynurenine pathway supports RQ but not *de novo* NAD^+ biosynthesis in helminths, and highlights promising pharmacological targets for helminthiasis.

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Synapse organization and circuit function of dual-transmitter neurons

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A single neuron can use more than one neurotransmitter to signal with neighboring cells and regulate behavior. These dual-transmitter neurons can segregate molecularly distinct presynaptic terminals within the same neuron, but little is known about what are the cellular and molecular strategies that differentially regulate neurotransmitter-specific synaptic pools and how this intracellular specificity shapes circuit function. My work aims to establish an *in vivo* model of dual-transmitter neurons using the well-mapped nervous system of the nematode *Caenorhabditis elegans* to understand how molecularly distinct synapses organize and segregate within a single neuron to regulate animal behavior. To visualize neurotransmitter-specific pools, we have developed tools to monitor the endogenous vesicular transporters of each neurotransmitter, which allow us to systematically validate *in vivo* the dual-transmission capacity of *C. elegans* neurons. Because the *C. elegans* nervous system has several neurons with dual-transmission capacity, the strategies I will develop could be readily implemented to any other neuron and broaden our understanding on how these dual-transmitter neurons assemble within functional circuits.
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Neuro-immune responses and transgenerational epigenetic inheritance of *Caenorhabditis elegans* against *Candida albicans* infection

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In its natural habitat, when *Caenorhabditis elegans* consumes harmful bacteria, its intestine is colonized, triggering responses that include the activation of the immune system and the nervous system to clear the infection, to escape from the pathogen and to remember avoiding it the next time is near. Depending on the pathogen, this learned information is transmitted epigenetically to the next generations as part of the strategies to improve survival of the progeny.
Using the powerful genetics and simple yet evolutionarily conserved systems of *C. elegans*, we aim to describe the immune and neuronal pathways, behavioral responses as well as mechanisms of transgenerational epigenetic inheritance of exposure to fungi, like the human pathogen *Candida albicans.* Presenting a choice of microbial foods to *naïve C. elegans,* we observed a strong preference for *C. albicans* over the non-pathogenic *Escherichia coli* OP50, or even the pathogenic bacteria *Pseudomonas aeruginosa*. Subsequently, within 4-6 h, *C. elegans* escapes the *C. albicans* lawn, in correlation with distension of the anterior part of the nematode's intestine. In addition, the population of *C. elegans* in contact with *C. albicans* for more than 4 h learns to avoid this specific yeast in future encounters, and this learned avoidance behavior is transmitted epigenetically to its progeny for one to four generations.
Our findings suggest that the responses to *C. albicans* mimic mechanisms involved after the infection with *P. aeruginosa* as well as *Enterococcus faecalis*. Future studies will reveal unique pathways to this eukaryotic pathogen.

Neuronal membrane glycoprotein (NMGP-1) is required for stress response in *Caenorhabditis elegans*

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Exposure to chronic stress causes changes in gene expression in organisms. One of the genes modulated by stress is *Gpm6a*, whose levels are decreased by stress and are reversed by the administration of antidepressants. GPM6A is a neuronal protein involved in plasticity and synaptogenesis. However, the role of GPM6A in the stress response is not yet known. Since NMGP-1 is a functional ortholog of GPM6A in *Caenorhabditis elegans*, we aimed to investigate the role of GPM6A in the stress response in this model.
First, using GFP expression and the NeuroPal strain, we identified that NMGP-1 is expressed both within and outside of nervous system tissues. We saw GFP expression in pharyngeal, amphid and phasmid sensory neurons. Next, using two *nmgp-1* mutants and RNAi, we investigated *nmgp-1* requirements under different paradigms: thermal, osmotic and oxidative (with paraquat) stress. We found that the lack of *nmgp-1* affects the survival of worms exposed to different stressors and intensities. Thus, *nmgp-1* in *C. elegans* is necessary for the stress response. Finally, we analyzed the modulation of *nmgp-1* by drugs used to treat neuropsychiatric pathologies. To this, the *nmgp-1* expression was evaluated in the "anhedonic" strain [CB246 *unc-64(e246)*]. We found that when the "anhedonic" state was reversed with olanzapine, *nmgp-1* levels increased. This preliminary result indicates the

potential utility of this gene and *C. elegans* to model mood disorders and may represent an attractive platform for screening new drugs to treat these pathologies using *nmgp-1* as biological marker.

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Ketogenic modulation of GABAergic signaling in *C. elegans*

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Mutations in PTEN (a negative regulator of the PI3K pathway) are associated with neurodevelopmental disorders, epilepsy, and schizophrenia. Several reports suggest that an increase in the excitation/inhibition ratio in the brain is a hallmark of these disorders. The *C. elegans* NM system, where both excitatory (ACh) and inhibitory (GABA) neurons innervate muscles, provides a suitable model for studying E/I balance. We found that *daf-18* (*C. elegans* ortholog for PTEN) mutants are hypersensitive to cholinergic drugs, suggesting a deficit in GABAergic signaling. *daf-18* mutants are deficient in eliciting complex movements such as the “omega turn”, a sharp turn in which the GABAergic inhibition on dorsal muscles plays a critical role. Moreover, *daf-18* mutants exhibit morphological defects in GABAergic neurons. DAF-18 specific rescue in GABAergic neurons partially rescued the defective phenotypes, suggesting an autonomic role of the PI3K pathway in GABAergic function. In addition, we found that the GABAergic deficit in *daf-18* mutants is entirely dependent on the inactivation of the transcription factor DAF-16/FOXO. Ketogenic Diets (KDs) have been used since the 1920s for epilepsy who were refractory to GABAergic medications. The mechanisms underlying this therapeutic effect remain elusive. We found that exposure to the ketone body hydroxybutyrate (βHB) during early development ameliorated GABA defects in *daf-18* mutants. Interestingly, this ketone body does not alleviate the defects observed in *daf-16*/FOXO mutants, suggesting an essential role of this transcription factor in the βHB effect. This study may contribute to the understanding of the fundamentals of disorders associated with imbalances between E/I signals.

Exploring age related effects on the lipid metabolism of a *Caenorhabditis elegans* model of Parkinson's disease

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Lipid homeostasis is essential for proper neuronal development and function, in fact, most neurodegenerative diseases are associated with lipid metabolism dysregulation, including Parkinson's Disease (PD). One of the hallmarks of PD is the presence of cytoplasmic inclusions in dopaminergic neurons. These amyloid aggregates are highly rich in the protein alpha-synuclein (αSyn), and its formation is triggered by changes in αSyn folding and assembly. However the molecular mechanisms which cause αSyn to misfold are not clearly understood. Several studies showed that certain lipids induce the formation of pathogenic αSyn conformations. Unsaturated fatty acids (UFAs), in particular, interact with αSyn and this interaction may be implicated in PD pathogenesis as well as in regulation of UFAs metabolism.
Given that lipid pathways are associated to PD pathogenesis, and that most of them are altered by aging it is important to understand the association between UFAs and αSyn in an experimental system that accurately recapitulates the biochemical changes that occur within a live aging organism. Accordingly, we chose to work with a *Caenorhabditis elegans* line that overexpress human αSyn in body wall muscle cells as animal PD models. By applying novel *in vivo* multidimensional NMR methodologies in control and αSyn overexpressing worms, in different age stages, we can obtain high resolution NMR spectra that pictures the worms' lipid profile at molecular resolution. This approach will allow us to gain insight about the effects of αSyn on lipids composition and behavior during PD onset and progression.

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The assembly of bacteria living in natural environments shape neuronal integrity and behavioral outputs in *C. elegans*

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Bacterivore nematodes are the most abundant animals in the biosphere, largely contributing to global biogeochemistry. Thus, the effects of environmental microbes on nematode's life history traits is likely to contribute to the general health of the biosphere. *Caenorhabditis elegans* is an excellent model to study the behavioral and physiological outputs of microbial diets. However, the effects of complex natural bacterial assemblies have only recently been reported, as most studies are carried out on monoxenic cultures of laboratory reared-bacteria. Here, we quantified physiological, phenotypical and behavioral traits of *C. elegans* feeding on two bacteria that co-isolated with wild nematodes from a soil sample. These bacteria were identified as a putative novel species of Stenotrophomonas named Stenotrophomonas sp. Iso1 and a strain of *Bacillus pumilus* designated Iso2. The distinctive behaviors and development patterns observed in animals fed with individual isolates changed when bacteria were mixed. We studied in more depth the degeneration rate of the touch circuit of *C. elegans* and show that *B. pumilus* alone is protective while the mix with Stenotrophomonas sp. is degenerative. The analysis of the metabolite content of each isolate and their combination identified NAD^+ as potentially neuroprotective. In vivo supplementation shows that NAD^+ restores neuroprotection to the mixes and also to individual non-protective bacteria. Our results highlight the distinctive physiological effects of bacteria resembling native diets in a multicomponent scenario rather than using single isolates on nematodes.

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Cannabinoids activate the insulin pathway to modulate mobilization of cholesterol in *Caenorhabditis elegans*

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Cholesterol is an essential lipid constituent of eukaryotic cell membranes. Furthermore, its derivated metabolites have important biological roles as signalling molecules. Because of its relevance, impairment in cholesterol metabolism has been related to several pathologies such as diabetes, cancer, among others. *Caenorhabditis elegans* is an useful model organism to study pathologies which have impaired cholesterol metabolism for the reason that this worm has homologous of 40% of genes that are associated with human diseases. Besides, *C. elegans* is auxotrophic for sterols and requires exogenous addition of them to survive. Cholesterol depletion leads to an early developmental arrest due to its essential role as precursor of signalling molecules. Thus, tight regulation of cholesterol storage and distribution within the organism is critical. We have recently demonstrated that the endocannabinoid 2-arachidonoylglycerol (2-AG) plays a key role in *C. elegans* modulating sterol mobilization. However, the mechanism by which 2-AG controls cholesterol trafficking in *C. elegans* is not known. Here we show that the calcium-activated regulator of neural dense-core vesicle exocytosis (DCVs) UNC-31 is essential for 2-AG-mediated stimulation of cholesterol mobilization. This, combined with mutant analysis, suggested that 2-AG-dependent cholesterol traffic requires signaling of insulin peptides through the DAF-2 insulin receptor. In addition, mutations in the *ocr-2* and *osm-9* genes coding for transient receptors potential type V (TRPV) ion channels, dramatically reduces the effect of 2-AG in cholesterol mobilization. These findings indicate that 2-AG act as endogenous modulators of TRPV signal transduction to control intracellular sterol traffic through modulation modulation of the IGF-1 signaling pathway.

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Keywords: C. elegans, endocannabinoid, genetic analysis, cholesterol, RNAi enhancer screen insulin pathway

Monthly Ecotoxicological Assessment of medium Uruguay River - Brazil using *Caenorhabditis elegans* as a biomonitor

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The Uruguay River is part of a relevant South American watershed that extends from Brazil to Uruguay and Argentina. Most of the regions bathed by the river are characterized by intense agro-industrial activity. The intense use of pesticides, associated with other factors, exposes the River to high chances of pollution. This study aimed to analyze changes in water samples collected for 12 months (January 2019-January 2020) in the municipality of Uruguaiana - BR, a city known for rice production. The physical-chemical parameters, pH, dissolved oxygen, conductivity and temperature during collections were also evaluated. We used the free-living nematode *Caenorhabditis elegans*, N2 wild-type worms were exposed for 24 hours to the samples containing *E.coli OP50* under constant agitation and then transferred to solid NGM medium for survival, longevity, reproduction and body length assays. For statistics, we used one-way or two-way ANOVA with Tukey's post hoc and a $p < 0.05$ was considered significant. We observed that the samples caused a reduction in worms survival in February, March, April, June, July, August and November, longevity was reduced in all months except January and February, impaired reproduction in the January sample and body size following exposures to May, August and November samples. We also quantified the levels of pesticides and metals in the samples, where the presence of Imazethapir, Sulfentrazone and 2,4-D were detected in February, March and September samples. Therefore, tour study highlights he importance of frequent studies in the area of ecotoxicology, due to constant pollution and environmental impacts.

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A microfluidic device for simple quantification of chemotaxis with *Caenorhabditis elegans* in neurotoxicological studies

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Nowadays, toxicology must meet two opposing demands: the analysis of a growing list of chemicals, and the resource limitations and ethical concerns associated with traditional mammalian testing. In this sense, *Caenorhabditis elegans* is a useful neurotoxicological model that has been successfully used to study human neurodegenerative disorder like Parkinson's disease. *C. elegans* is able to detect external chemical signals and perform chemotaxis behaviors through its simple chemosensory system. Here, we propose that the neurotoxic effect of xenobiotics could be reflected in the chemotaxis behavior of this nematode. Therefore, a Lab-on-a-Chip microfluidic device was designed to analyze chemotaxis in *C. elegans* and a rapid protocol was established to be used in the neurotoxic agent detection. As proof-of-principle, synchronized L1-larvae were exposed to four pesticides for 72 h (Paraquat 0.05 mg/L, Glyphosate 0.1 mg/L, Cypermethrin 0.1mg/L and ʎ-Cyhalothrin 0.1 mg/L) and the chemoattraction to 2-butanone was evaluated with the microfluidic device. The nematodes reaction to 2-butanone were registered every 30 minutes for 3 hours and a chemotaxis index (CI) between a range of -1 to 1 was calculated to indicate avoidance, indifference or attraction. In the control group without pesticides treatment, the maximum attraction of the nematodes to 2-butanone was observed 150 minutes after starting the chemotaxis test (CI 0.6). Nevertheless, chemotaxis was inhibited by treatment the nematodes with Paraquat (CI 0.2), Glyphosate (CI -0.2), Cypermethrin (CI 0.5) and ʎ-cyhalothrin (0.2). These results demonstrated that this device may therefore serve as rapid platform to analyze chemotaxis behaviors and detection of neurotoxic agents.

Mathematical modeling of microRNA-Transcription Factor networks in *Caenorhabditis elegans* exposed to high-glucose diets.

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Diets influence lifespan in all organisms. In *C. elegans* as well as in other animals dietary restriction increases it, while high-glucose diets (HGD) decrease it. Transcription Factors (TF) from the Insulin/IGF-1 and TOR signaling pathways have been reported to be involved. Additionally, several microRNAs are known to regulate the expression of these TFs. TF and microRNA expression are changed according to the diet of the worms and there is a gap in understanding on what are the basis of the differential expression observed.
Boolean networks (BN) refer to a class of mathematical models based on logical rules that allow the analysis of complex biological regulatory networks. BN are graphs where nodes represent genes and edges are regulatory interactions defined as Boolean functions or logic gates that are used to mimic cellular physiology observed in experiments. Perturbation of the system allows the discovery of causal links within the complex network. These models are constructed from experimental data and generate different dynamics that converge to steady states named attractors. Each attractor is associated with one phenotype.
In this project we developed a regulatory network of microRNAs and FTs that change their expression when the worm is grown in HGD. After analysis of the dynamics of this network, we successfully obtained attractors that are expected to arise in concordance to the experimental data reported. Furthermore, these attractors faithfully represent the active or inactive states of the genes considered to control the worm's lifespan showing causal relationships between diet and lifespan.

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Coupling between transcription and alternative splicing in *C. elegans*

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In eukaryotic cells, the RNA molecule resulting from transcription contains both coding (exon) and noncoding (intron) sequences. Through the process of splicing the intron sequences are removed from the newly synthesized RNA: the mature RNA transcript is composed only of exon sequences. Alternative splicing is a process that explains how multiple mRNA variants can be produced from a single gene.
We have previously shown that light regulates alternative splicing in plants. The chloroplast control of nuclear alternative splicing in plants responds to the kinetic coupling mechanism found previously in mammalian cells. This model explains how changes in RNA polymerase II elongation rate influence alternative splicing choices.
Our goal is to study coupling between transcription and alternative splicing in whole organisms, using *C. elegans* as our model organism. We have chosen to study the effect of starvation on alternative splicing in L1 animals. Alternative splicing patterns of representative splicing events (hrpf-1 and uaf-1) show changes in response to starvation.
Furthermore, L1 animals were treated with camptothecin (a drug that inhibits transcription elongation): treatment with camptothecin increases hrpf-1 exon inclusion, whereas treatment with trichostatin A (drug that causes histone acetylation and therefore increased transcription elongation) produces the opposite effect on hrpf-1 splicing pattern. These results suggest that transcription elongation plays a role in this regulation of alternative splicing in C. elegans and that coupling is important for a whole organism to respond to environmental cues.

Germ cell fusion and apoptosis is induced by the phosphatidylserine biosynthesis pathway

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In *C. elegans*, and other organisms, many germ cells served as nurse cells to later be removed by apoptosis. However, some germ cells are also eliminated due to defects, for example, when they are fused by an unknown mechanism. We and others have also observed that different types of stress trigger germ cell apoptosis. To test if stress triggers germ cell fusion, we subjected one-day-old nematodes to heat shock (3h at 31°C), starvation (6h without bacteria), or paraquat (100 mM, 1h). After stress, gonads were dissected and nuclear morphology was assessed by DAPI staining. We observed that the gonads of animals exposed to heat shock, starvation, or oxidative stress showed an increase of binucleated germ cells in contrast to control wild-type animals. To gain insights into the mechanism of germ cell fusion, we made a screening, by RNAi, to test different pathways that have been shown to affect cell fusion in other organisms. We found that the phosphatidylserine biosynthesis pathway plays an important role in germ cell fusion and apoptosis. Additionally, we found that stress caused gonad structural changes; in particular, gonad rachis reduction, germ cell swelling, and/or stacking. We observed that gonad structure alterations upon stress lead to a reduction in the cytoplasmic flow that normally feeds oocytes that are undergoing maturation. Gonad changes were reversible when stress was eliminated. Our work demonstrates that during stress the phosphatidylserine biosynthesis pathway induces germ-cell fusion and apoptosis.

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The RNA binding protein GLA-3 is important to protect germ cells from stress

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mRNA turnover is essential to control gene expression. In mammals, the tristetraprolin (TTP)family includes the RNA binding proteins TTP and TIS11. These proteins bind to AU rich elements(AREs) in their mRNA targets to recruit the deadenylation complex CCR4-NOT promoting their degradation. Among their main targets for TTP are mRNAs that encode for cytokinesis like TNF-alpha, which regulate the inflammatory response; therefore mice mutant for TTP develop autoimmune diseases. TTP is associated with processing bodies and stress granules, and it is important for their formation. In *Caenorhabditis elegans*, GLA-3 is one of the TTP homologous and our aim is to study its function in the stress response. We have found that loss of *gla-3* function presents different alterations like increased germ cell apoptosis, severe defects in meiosis progression, reduced brood size and a low frequency of embryonic lethality. *gla-3* mutant animals are unable to form stress granules and their germ cells are more sensitive to heat shock. Unexpectedly, we found that GLA-3 does not conserve the structure to bind to the AREs sites nor has the domain that recruits the CCR4-NOT complex. These results predict that GLA-3 does not participate in mRNA degradation as its homolog TTP does.

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Rhodoquinone as a key molecule for sulfide, cyanide and pathogen response in *C. elegans*

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Animals facing hypoxic or anoxic conditions need a mechanism to obtain energy without using oxygen. A biochemical adaptation of some animals to hypoxia is an alternative mitochondrial electron transport chain (CTEM), in which rhodoquinone (RQ) and not ubiquinone (UQ) is the lipidic electron carrier and fumarate, and not oxygen, is the final electron acceptor.
Our results suggest that in *C. elegans* RQ does not have an essential role in the hypoxia conditions examined, raising the question of whether RQ serves another role in *C. elegans*. In its natural environment, this organism can encounter high concentrations of hydrogen sulfide (H_2S), as well as pathogenic bacteria that kill the worm by the production of hydrogen cyanide (HCN). H_2S and HCN are inhibitors of complex IV of the canonical CTEM, preventing oxygen from being used as the final electron acceptor. Therefore, a possible additional role for RQ could be its participation in the worm defense against these toxic compounds. In fact, mutant strains that do not synthesize RQ (and do synthesize UQ) do not survive in the presence of both HCN and H_2S high concentration and are more sensitive against the pathogenic bacteria *Pseudomonas aeruginosa* PA01 (which kills the worm by generating HCN), compared to both the wild type strain and UQ-less worms. These results suggest a new role for RQ in protecting the worm from poisoning with HCN and H_2S produced by pathogens present in the worm's habitat.

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Evaluation of MRSA virulence of structure-based drug against the lipoic acid salvage pathway using *Caenorhabditis elegans*.

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Methicillin resistant *Staphylococcus aureus* (MSRA) is an important human opportunistic pathogen responsible for a broad spectrum of diseases ranging from minor skin lesions to life-threatening postsurgical infections in humans. The versatility of *S. aureus* as a pathogen hinges on its release of virulence factors that compromise host immune defenses and on its capacity to adapt to host nutritional restriction by incorporating essential nutrients. Lipoic acid (LA) is a universally conserved sulfur-containing cofactor required for intermediary metabolism. *S. aureus* employs a "lipoyl-relay" pathway for *de novo* biosynthesis and salvage of this cofactor. It encodes two lipoate ligases, LplA1 and LplA2, a lipoyl-carrier protein (GcvH) and an amidotransferase, involved in LA rescue during infection. In this work, we performed a phenotypic screen of different molecules that were identified by a virtual screen against LplA2. We selected a compound, lpl-004, that caused a marked growth inhibition of the WT strain in minimal medium. This effect was less severe in Δ*lplA1* or Δ*lplA2* single mutants, while the growth of the double mutant Δ*lplA1* Δ*lplA2* was not affected. Using protein extracts of different bacterial mutants, we determined that lpl-004 would be bound to E2s. To test the effect of the treatment on *S. aureus* virulence we determined the lifespan of worms, using USA_300 grown in rich medium with and without the addition of lpl-004 as supplement. The observed increase in worm lifespan suggests that this compound could be useful for a combinatorial drug therapy against this pathogenic bacterium.

Born to be a wild worm: differential circadian rhythms between domesticated N2 and wild *Caenorhabditis elegans* isolates

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Circadian rhythms represent an adaptive feature, ubiquitously found in nature, which grants living beings the ability to anticipate daily variations in their environment. The nematode *C. elegans* provides an excellent model for genetics and neuro-behavioral studies and is currently used as a novel model for circadian research. The strain of *C. elegans* currently used in laboratories is the N2, and is considered a domesticated or laboratory strain. Various studies show that recent isolates of *C. elegans* are highly divergent at the genomic level with respect to the N2 strain due to the accumulation of numerous mutations. In this work, using a locomotor activity recording system we present a circadian screening of wild *C. elegans* isolates. Our results show that the N2, MY23, DL238 and the wild JU1652 strain populations were synchronized to a cold-warm (CW) cycle. MY23 tended to be truly synchronized to the zeitgeber, while the other worm strains (especially the control N2 strain) show varying degrees of masking. Indeed, ~50% of the N2 strain populations were synchronized to a CW cycle, increasing to 73% and 69% in the wild MY23 and DL238 strain populations, respectively. All strains retained circadian rhythms of ~24 h under constant conditions, except strain JU1652 which had a circadian period of ~23 h. Circadian characterization of wild *C. elegans* isolates, together with genomic data, would make it possible to identify genomic regions (or even genes) involved in synchronization.

MyTH-FERM Myosins in the C. elegans Intestine

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The intestinal epithelium serves critical roles both in nutrient absorption and as a protective barrier against pathogenic infection. The barrier function critically depends on the formation of tight links between microvilli. These are known to be cadherin-based linkages found at the tip of microvilli that are anchored to the actin cytoskeleton by a MyTH-FERM myosin, Myo7B, in the mammalian intestinal epithelium. C. elegans expresses two MyTH-FERM myosins, hum-6 (a Myo7) and hum-4 (a Myo15). These myosins are characterized by the presence of two MyTH-FERM domains in their C-terminal tail region that are known to be sites of partner binding. The available deletion mutants (ok136, ok632 - hum-6, ok440 - hum-4) exhibit normal fertility, viability, chemotaxis, touch response and crawling. Injection of fosmids carrying GFP-fusions of each myosin into N2 worms revealed that HUM-6 is exclusively expressed in the intestine, all along the apical region of the epithelium. Interestingly, HUM-4 is also found in the intestine, with a localization pattern similar to that of HUM-6. This suggests that these myosins could similarly serve to maintain the microvillar barrier function in the worm intestine to protect the epithelium from pathogenic infection.

Unravelling the physiological role and molecular function of Caenorhabditis elegans betaine-sensitive nicotinic receptors.

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Parasitic nematodes have acquired resistance to anthelmintic drugs, generating problems in human and animal health. The elucidation of function and drug selectivity of their targets is essential for the development of novel drugs. Nicotinic receptors (nAChRs) are involved in worm locomotion and are targets of anthelmintic drugs. The broad-spectrum nematocidal drug monepantel (MNP), which belongs to a new class of compounds, targets ACR-23 nAChR. ACR-23, whose endogenous agonist is betaine (BE), is present in muscle and neuronal cells of nematodes and since it is not conserved in vertebrates it is an interesting pharmacological target. We use the free-living nematode *Caenorhabditis elegans* as a model of parasitic nematodes to explore ACR-23 as a novel drug target. By performing locomotion assays with wild-type adult worms we showed that exogenous BE significantly increased worm motility. This effect was not observed in *acr-23* mutants, indicating that the enhancement of ACR-23 activity causes worm hypermotility. The exposure of worms to MNP produced the opposite effect, resulting in reduced motility as a function of concentration (EC_{50} = 50 μM). MNP induced spastic paralysis and inhibited egg hatching, indicating important anthelmintic ability. Locomotion assays with mutant worms demonstrated that MNP-induced paralysis is mediated by ACR-23 and DEG-3/DES-2 nAChRs. By patch-clamp recordings from cultured *C. elegans* muscle cells, we described for the first time the properties of BE-elicited single-channel and macroscopic currents and the modulation by MNP. Our study provides insights into the molecular basis of anthelmintic action, which pave the way for the development of novel drugs.

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Behavioral changes induced by starvation and hyperglycemia in *C. elegans*

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All organisms must sense and adapt to the ever-changing environmental conditions to favor their survival. *C. elegans* have an extraordinary capacity to sense molecules such as odorants that allow them to adapt their behavior and survive the changing environment. Additionally, they can establish long-term memory of the favorable environments in favor of survival. In our laboratory, we are interested in exploring how different environments such as starvation, hyperglycemia, inflammation or metabolic challenges affect the epigenome and how this translates into behavioral changes. We explore different model systems including the nematode *C. elegans* where we have defined that starvation induces changes in the worm's preference for odorants. These changes depend on several mechanisms, including the insulin pathway, small RNA (sRNA), histone methylation and expression of the transcription factor CREB. Interestingly, starvation induces CREB expression not only in neurons but also in intestinal cells. On the other hand, exposure to a hyperglycemic environment impairs the ability of *C. elegans* to establish an associative memory between food and odorants and changes the worm's preference for odorants. This event also depends on CREB expression and sRNA metabolism. Our results highlight the intricate relationship between different environments and their association with transcriptional regulation and suggest crosstalk between neurons and intestinal cells in the worm.

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Genetic and molecular features of P. aeruginosa-induced ribosome cleavage

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The bacterium *Pseudomonas aeruginosa* induces translation inhibition in multiple hosts by at least two routes. The first route is mediated by the post-translational modification of translation elongation factor 2 [1]. The second one relies on the cleavage of host ribosomes at helix 69 (H69) [2], a highly conserved rRNA hairpin critical for mRNA decoding and subunit joining. The ribosome cleavage strategy requires the bacterial quorum sensing system and host endocytosis, but the molecular mechanism of H69 cleavage is unknown.

Addressing this knowledge gap through genetic analysis, we screened candidate host and bacterial nucleases. We found that the loss of either dis-3, pqe-1, tsn-1 or hoe-1 results in reduced levels of ribosome cleavage upon infection, suggesting that these genes contribute to ribosome cleavage either directly or indirectly.

Lysates from infected worms contain the activity that cleaves H69 [2]. This activity cuts H69 in C. elegans [2] and rabbit ribosomes but not in those of E. coli. Also, the activity does not cofractionate with and is not competed by exogenously added H69 RNA hairpin. These results suggest that the H69 nuclease requires elements of the eukaryotic ribosome other than the target's RNA sequence to elicit its activity. Finally, we have found that the activity is amenable to biochemical fractionation, as it elutes into single activity peaks when separated using size-exclusion, cation exchange, heparin column and ammonium sulfate precipitation approaches.

Neural modulation of systemic stress response requires the insulin like-peptide INS-3

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Throughout the animal kingdom, the perpetuation of the flight response leads to reduced ability to cope with environmental challenges, a drastic lifespan reduction, and an increase in disease susceptibility. We showed that, in *C. elegans*, the tyraminergic neuron RIM supplies a state-dependent neural switch between acute flight and long-term environmental stress responses. During the flight-stress response RIM neurons release TA, which stimulates the intestinal adrenergic-like receptor TYRA-3. This leads to DAF-2/Insulin/IGF-1 pathway activation and inhibition of cytoprotective mechanisms in the intestine and other tissues. We hypothesized that TYRA-3 stimulates the release of Insulin-Like Peptides (ILPs) from the intestine that can systemically activate the DAF-2 insulin/IGF1 receptors. We focused on strong agonist ILPs that are expressed in the intestine (INS-3, -4, -6, -32, and DAF-28). We found that *ins-3* mutants are resistant to both heat and oxidative stress, much like *tyra-3* mutants. Moreover, *ins-3* mutants are resistant to the impairment of stress resistance upon exposure to exogenous tyramine. In addition, *ins-3;tyra-3* double mutants are as resistant to environmental stress as single mutants, suggesting that both genes act in the same pathway. Since *ins-3* is expressed in neurons and the intestine, we performed tissue-specific rescue experiments. We found that expression of *ins-3* in the intestine restores stress resistance to wild-type levels. Taken together, our results suggest that intestinal activation of TYRA-3 by the escape neurohormone TA leads to INS-3 release which acts as an endocrine, autocrine, and/or paracrine signal to activate DAF-2 in different tissues.

1. Effect of chamomile, peppermint and citronella infusions on the model organism *Caenorhabditis elegans* exposed to hydrogen peroxide

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Infusions, in addition to their basic nutritional value and nutraceutical properties, provide health benefits, including the ability to prevent and treat diseases (Gastaldi et al. , 2018). That's why herbal teas are used as therapeutic vehicles of traditional and globally popular medicine (Poswal et al. , 2019). And with information obtained from model organisms such as the nematode *Caenorhabditis elegans* (*C. elegans*), important phenomena are examined and extrapolated to species of interest, species that are more difficult to study directly. In this study, nematodes of the N2 strain (wild type) of synchronized age cultured in agar-NGM plates at 19 °C were used. An untreated group (CTL), an infusion-treated group (Chamomile [MZ], Peppermint [HB] or Citronella [CN]), a hydrogen peroxide-exposed group (H_2O_2) and an infusion-exposed group (H_2O_2 + MZ, HB or CN) were established. For survival trials, the worms were treated with H_2O_2 (10 µM). Live and dead worms were counted every hour for a period of 5 hours. With the resulting data, Kaplan-Meier curves were elaborated and analyzed using the Log-Rank test considering that a significant difference between curves is $P<0.05$. HB and MZ infusions confer antioxidant protection against the oxidative insult represented by exposure to hydrogen peroxide (0.5 mM). Coinciding in part with the theory that these herbal products proffer antioxidant properties. Finally, the usefulness of the model organism *C. elegans* has been shown as a fast response and affordable means for the study of nutraceutical products, whether new or already present on the market.

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2. Safety evaluation of graphene nanomaterials in *Caenorhabditis elegans*

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Graphene, a two-dimensional carbon nanomaterial, is a promising product to be used in chemical and electronic applications in the biomedical area, mainly due to its high electrical conductivity and mechanical resistance. Some studies indicate that carbon-containing materials can be harmful to living organisms, therefore, it is necessary to investigate the use of graphene in relation to toxicological effects and its environmental impacts. *Caenorhabditis elegans* is an alternative model widely used in the field of toxicology, due to its many advantages such as short lifespan, small size, easy maintenance and handling, and rapid reproduction. Therefore, the objective of this work is to evaluate and compare the safety of graphene and graphene-nickel nanomaterials in *C. elegans*. The strain used in the study was N2 (wild type), maintained in NGM medium ("nematode growth media") and *E. coli* OP50 bacteria. The worms were synchronized, in order to break the cuticle and obtain eggs, and were treated in the L1 stage, acutely (30 minutes) at concentrations of 0.1, 1 and 5 $\mu g.L^{-1}$. After 48 hours of the end of treatment, the survival rate, body size, area, progeny size and integrity of the intestinal membrane were analyzed. The results of all parameters analyzed did not show significant changes in relation to the control in any of the tested concentrations, which may indicate a possible safety in the use of these nanomaterials. In view of this, other analyzes related to the toxicity of graphene must be carried out to confirm the data obtained so far.

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3. 1-Mesityl-3-(3-Sulfonatopropyl) Imidazolium Protects Against Oxidative Stress and Delays Proteotoxicity in *C. elegans*

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Due to the increase in life expectancy, age-related neurodegenerative diseases (NDs) have become more prevalent. Conventional treatments fail to arrest or delay neuronal proteotoxicity that characterizes these diseases. Due to their diverse biological activities, imidazole rings are intensively explored as powerful scaffolds for the development of new bioactive molecules. By using *C. elegans*, our work aims to explore novel biological roles for these compounds. To this end, we have tested the *in vivo* anti-proteotoxic effects of imidazolium salts. Since NDs have been largely linked to impaired antioxidant defense mechanisms, we focused on 1-Mesityl-3-(3-sulfonatopropyl) imidazolium (MSI), one of the imidazolium salts that we identified as capable of improving iron-induced oxidative stress resistance in wild-type animals. By combining mutant and gene expression analysis we have determined that this protective effect depends on the activation of the Heat Shock Transcription Factor (HSF-1), whereas it is independent of other canonical cytoprotective molecules such as abnormal Dauer Formation-16 (DAF-16/FOXO) and Skinhead-1 (SKN-1/Nrf2). To delve deeper into the biological roles of MSI, we analyzed its impact on previously established *C. elegans* models of protein aggregation. We found that MSI ameliorates β-amyloid-induced paralysis in worms expressing the pathological protein involved in Alzheimer's Disease. Moreover, MSI also delays age-related locomotion decline in other proteotoxic *C. elegans* models, suggesting a broad protective effect. Taken

together, our results point to MSI as a promising anti-proteotoxic compound and provide proof of concept of the potential of imidazole derivatives in the development of novel therapies to retard age-related proteotoxic diseases.

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4. Effects of inactivation on UNC-49 receptor by heat stress in model organism *Caenorhabditis elegans*

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Earlier, *C. elegans* research to clarify the endocrine physiology has been focus on regulatory mechanisms of stress response. These mechanisms are conserved in evolution, suggesting a common hormonal mechanism in control of ageing and stress. Among these mechanisms, insulin/IGF-1 signalling (IIS) pathway is central in topics as reproduction, stress resistance and Dauer stage, besides of extenting life-span. The aim of this study was to determine the influence of heat shock stress (HS) on GABAergic activity in *C. elegans*. For this purpose, we tested the effect of exposure to picrotoxin (PTX), gammaaminobutyric acid (GABA), hydrogen peroxide, and HS on the

occurrence of a shrinking response (SR) after nose touch stimulus in N2 (WT) worms. Moreover, the effect of HS on the expression of UNC-49 (GABAA receptor ortholog) in the EG1653 strain and the effect of GABA and PTX exposure on HSP-16.2 expression in the TJ375 strain were analyzed. PTX 1 mM- or H_2O_2 0.7 mM-exposed worms displayed a SR in about 80 % of trials. GABA exposure did not cause a SR. HS prompted the occurrence of a SR as did PTX 1 mM or H_2O_2 0.7 mM exposure. In addition, HS increased UNC-49 expression, and PTX augmented HSP-16.2 expression. Thus, the results suggest that oxidative stress, through either H_2O_2 exposure or application of heat shock, inactivates the GABAergic system, which subsequently would affect the oxidative stress response, perhaps by enhancing the activity of transcription factors DAF-16 and HSF-1, both regulated by the IIS pathway and related to HSP-16.2 expression.

5. Stress-induced germ cell apoptosis, but no stress granules formation, is observed when *C. elegans* is exposed to chemotherapy agents

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In our laboratory, we are studying how germ cells respond to different stress conditions. The *C. elegans* gonad is an excellent model because it is one of the biggest organs in the animal, is translucent and is a syncytium allowing us to observe different phenomena in live animals. We and other groups have observed that when *C. elegans* germ cells are subjected to stress, germ cell apoptosis is activated and stress granules (SGs) are formed in the gonad. SGs are biomolecular condensates separated by liquid-liquid condensation in which presumably molecules are protected from stress although their actual function is still unknown particularly in *C. elegans*.

Our aim is to study how *C. elegans* germ cells respond to different chemotherapeutic agents to elucidate the mechanisms that regulate these responses. In cancer cell lines, the use of chemotherapeutic agents induces the assembly of SGs, which presumably makes them more resistant to the treatments. Additionally SGs can inhibit stress-induced cell death by entrapping proteins involved in apoptosis. We are exposing nematodes to chemotherapeutic agents like cisplatin, etoposide and paclitaxel. Until now, we have observed that germ cell apoptosis increases upon exposure to the tested chemotherapeutic agents but we have failed to detect SGs formation. We will expose animals to higher concentrations of chemotherapy agents to see if SGs are formed in the gonad because our aim is to study their correlation with apoptosis. We will continue studying the pathways that induce germ cell apoptosis upon exposure to chemotherapeutic agents.

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6. Effects of temperature on mechanosensation and neurodegeneration

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Mechanotransduction is a fundamental process underlying the senses of touch, balance, proprioception and hearing. In *C. elegans*, MEC-4, a DEG/ENaC family protein is the pore forming unit of the mechanosensory channel complex, expressed in the Touch Receptor Neurons (TRNs). A gain of function mutation (A713V) in MEC-4 located in residues near transmembrane segment 2 (MEC-4d), causes the unregulated entry of Na^+ and Ca^{2+} and the concomitant degeneration of the TRNs. Previous unpublished observations from our group revealed that gentle touch response and TRN degeneration are affected by temperature changes in the range of 15 to 25°C, such that warmer temperatures both decreases responsiveness of the nematode and that TRNs bearing the MEC-4d channel are protected from premature degeneration. Our results show that the response to gentle touch in wild type nematodes maintained at 25°C is diminished (5/10) compared to 20°C (9/10) or 15°C (10/10). At the same time the neurodegeneration rate is lower at 25°C with functional axons reaching 94% after 96 hours, compared to 15°C where animals have fully degenerated axons, consistent with the constitutively open MEC-4d channel. These results suggest that the mechanotransduction complex is sensitive to environmental temperature. Effects of temperature on DegENaC channels have not been reported and we do not know where the temperature sensitivity comes from. In the future we expect to test the different subunits dependence on temperature by heterologous expression of the complex in Oocyte eggs and by direct patch clamp on touch cells in culture.

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7. Liposomes loaded with bougainvillea Glabra Choisy Bracts extract reduce the hyperplasia and extends the longevity in a *C. elegans* cancer model

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Cancer is responsible for high mortality rates in the population. Therefore, it is necessary to search for new compounds that are safe and that have molecular action in the pathways involved in the cancer development. In *Caenorhabditis elegans* (*C.elegans*), the gene *let-60* is homologous to Ras in humans, and the worms that present the gain-function (*gf*) in this gene develop the multivulva phenotype (*Muv)*. We used the strain MT4244 [*unc-24*(e138) *let-60*(n1046) IV] to verify the safety and efficacy of liposomes loaded with *Bougainvillea glabra* Choisy bracts extract (BGC). After chronic treatment we verified that the BGC was safe at the concentrations tested (10, 50, 75 and 100 µg/mL of Chlorogenic Acid Equivalents-CAE). In addition, BGC promoted a reduction in the area of the tumors (*Muv phenotype*) in the third day of adult worms with extension of longevity. In the strain MD701[*lim-7p*::*ced-1*::GFP + *lin-15*(+)], the number of apoptotic cells in the germline cells increased. This evidence of apoptosis signaling might not due to a toxic response of BGC, once in the strain CL2166 [(pAF15)*gst-4p*::GFP::NLS] only the highest concentration increased fluorescence intensity of the enzyme GST-4 (Glutathione-S-transferase) expression. When we evaluated the DAF-16 localization, using the strain TJ356 [*daf-16p*::*daf-16a*/b::GFP + *rol-6*(su1006)], we verified an increase in the nuclear translocation of this transcription factor. The results suggest that BGC can attenuate the formation of the *Muv* phenotype in *let-60* mutants through apoptotic activation, which promotes the lifespan extension in the worms.

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8. Role of unsaturated fatty acids in alpha-synuclein aggregation in a Caenorhabditis elegans model of Parkinson disease

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Parkinson disease (PD) is a common and incurable neurodegenerative disorder. *Caenorhabditis elegans* shows unique promise to evaluate PD phenotypes. The misfolding and aggregation of the protein alpha-synuclein (aSyn) into filamentous inclusions called Lewy bodies in dopaminergic neurons is a pathological hallmark of PD. Numerous reports indicate that aSyn interacts with lipids as part of its normal functioning; however, it has been shown that perturbations in lipid metabolism influence disease progression. In particular the oleic acid (OA), an unsaturated fatty acid (UFA), increased aSyn inclusion formation and toxicity in yeast and mammalian cell models and the inhibition of stearoyl-CoA-desaturase enzymes (SCD) reversed those features.
We work with an established *C. elegans* strain overexpressing human aSyn-YFP construct in muscle cells to characterize the *in vivo* aggregation of aSyn upon altering UFAs homeostasis, by microscopic assessment. We perform RNAi assays to block the expression of desaturase enzymes involved in polyunsaturated fatty acids (PUFAs) synthesis pathway. To test the effect of desaturases knockdown on the worm´s lipid content, we analyze the fatty acid composition by NMR spectroscopy.
We found that blocking the expression of one isoform of the SCDs (Fat-7) catalyzing the first committed step of PUFAs synthesis decreases aSyn aggregation. The exogenous addition of the Fat-7 product (OA) restores aSyn aggregate formation. This effect was not observed when we blocked expression of the Fat-3 desaturase that acts in a late step of PUFAs synthesis. These results suggest that the role of UFAs in aSyn aggregation is mediated by an early intermediate of PUFAs synthesis.

9. Tetragonisca stingless bee propolis fiebrigi has antioxidant activity in *Caenorhabditis elegans*

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Oxidative stress is an imbalance between the generation and neutralization of reactive species in the body that can trigger diseases such as Alzheimer's and cancer. Propolis, a resinous substance produced by several species of bees, has antioxidant properties described in the literature. This study aimed to evaluate the acute toxicity and antioxidant activity of the ethanolic extract of propolis from native stingless bees *Tetragonisca fiebrigi*, *in vivo*. The experiments were carried out with the N2 model of *Caenorhabditis elegans* at stage L4. To evaluate the acute toxicity, the animals were exposed to different concentrations of the extract (10–1500 µg / mL) for 24 and 48h. To verify the antioxidant activity, nematodes pre-treated with extract (50-1000 µg/ mL) for 1h were exposed to the stressor Juglone (40 µM) for 24 and 48 h. The viability of the animals was evaluated by stimulation with a platinum loop. Results are the average of three independent experiments in triplicate. Propolis extract did not promote acute toxicity in nematodes during the evaluated periods. The extract showed protection against oxidative damage from 100 µg/mL, reaching 83% viability at 500µg/mL, compared to the Juglone control, which showed 42,44% viability at 24 h of incubation. In 48 h, the extract showed significant antioxidant activity in all concentrations. In this context, we conclude that *T. fiebrigi propolis extract* has no toxicity and reduces the oxidative damage promoted by Juglone, and can be used in the prevention and/or alternative treatment for diseases related to oxidative stress.

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10. Evaluation of the reprotoxicity of pristine and UVC-degraded polystyrene nanoplastics in *Caenorhabditis elegans*.

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The increase of plastic production together with the incipient reuse/recycling system has resulted in massive discards in the environment allowing the formation of micro and nanoplastics (MNPs), recently detected in human blood and placenta. However, the effect of these materials on reproductive health has been poorly investigated and even less is known on the reprotoxicity of degraded/wild MNPs. The aim of this study was to evaluate the reprotoxicity potential of pristine 100 nm polystyrene nanoplastics (PSNP) or their UVC-degraded version (PSNP-UV) in *C. elegans*. To do that, L1 were exposed to different concentrations of PSNP/PSNP-UV (1, 100, 10,000 ng/mL) for 72h at 20°C. The number of fertilized eggs laid by worms exposed to PSNP-UV versus PSNP (100 or 10,000 ng/mL) was significantly lower, indicating exposure to PSNP-UV results in infertility in *C. elegans*. The number of unfertilized eggs laid by worms exposed to 10,000 ng/mL PSNP-UV was statistically higher than control-UV and PSNP (10,000 ng/mL). Embryonic lethality was statistically higher in nematodes exposed to 10,000 ng/mL PSNP when compared to control, as well as in hermaphrodites exposed to 100 or 10,000 ng/mL PSNP-UV (versus control-UV). The exposure to PSNP (100 or 10,000 ng/mL) and PSNP-UV (all concentrations) produced significant larval lethality versus respective control. Our preliminary data suggest that exposure to PSNP-UV results in worse reproductive performance compared to PSNP, potentially due to the detrimental effect of degradation products formed. More studies are needed to identify the mechanisms and chemical entities behind the reprotoxicity induced by UV-degraded PSNP.

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11. Aqueous extract of the stem bark of Lafoensia pacari protect Caenorhabditis elegans from oxidative stress

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Oxidative stress is the imbalance between the formation and neutralization of reactive species in the body, which can develop chronic diseases such as Alzheimer's disease and cancer. *Lafoensia pacari* (Lythraceae), popularly known as Dedaleira, is a brazilian cerrado tree described for its *in vitro* antioxidant activity. Therefore, the objective of this work was to investigate the *in vivo* toxicity and antioxidant activity of the aqueous extract of *L. pacari* bark (EALp). The tests were carried out with *Caenorhabditis elegans*, strain N2 in L4. To evaluate acute toxicity, the animals were exposed to different EALp concentrations (1-1,000 µg/mL) for 24 and 48 hours. To evaluate the antioxidant activity, the animals were pre-incubated with different EALp concentrations (2.5 – 500 µg/ml) for 1h, and exposed to Juglone (80µM) for 18h at 20 ºC. The animals were considered dead when they did not respond to the stimulus with a platinum wire. The results refer to the mean of 3 independent experiments (n=30). EALp showed no toxicity in the evaluated concentrations. The oxidative stress induced by Juglone reduced the animals viability to 17%. The treatment with EALp, except at the lowest investigated concentration, maintained the viability of the animals at 45% (25 µg/ml) and between 73 and 82% at higher concentrations (50-500 µg/ml). In summary, we conclude that EALp does not present toxicity at the evaluated concentrations, being able to protect animals from oxidative stress. Thus, further studies will be carried out to assess its potential in chronic diseases associated with oxidative stress.

12. Toxicity assessment of ferrous iron overload conditions in *Caenorhabditis elegans*

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The present study includes the assessment of the toxicity of formulated and nanoformulated ferrous compounds and the evaluation of the antioxidant ferrostatin-1 in the model organism *Caenorhabditis elegans*. The potential toxicity of $FeSO_4.7H_2O$ and $FeSO_4$ nanoparticles both at 0 mM concentrations; 0.5 mM; 1 mM; 1.5 mM and 2 mM was evaluated, analyzing the survival and locomotor activity of C. *elegans*. To this end, worms of the N2 strain in the L4 larval stage were exposed to both compounds in liquid K medium for one hour. Subsequently, mortality was evaluated and movement speed was recorded using the Microtracker SMART equipment (Phylumtech S.A., Argentina). The results show a dose-dependent increase in lethality in response to $FeSO_4.7H_2O$, which is reversed at all concentrations by pretreatment with ferrostatin-1. On the contrary, and probably due to their biocompatible coating, the ferrous nanoparticles showed mortality similar to that of the control animals (except for the 0.5 mM dose, which was higher). Regarding locomotion, a U-shaped decrease in speed was observed in response to $FeSO_4.7H_2O$, which was partially reversed by pretreatment with ferrostatin-1. On the contrary, the nanoformulation induced a dose-dependent increase in mobility. These data demonstrate the usefulness of the C. *elegans* model organism to demonstrate the toxicity resulting from ferrous iron overload, the ability to respond to antioxidants, and its sensitivity to identify differential effects according to the formulation.
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13. Evaluation of the toxicity and antioxidant protection of geopropolis from stingless bees from the Brazilian cerrado in *Caenorhabditis elegans*

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Geopropolis is a mixture of plant resins plus soil, produced by stingless bees. This bioproduct is used in traditional medicine by Amazonian and indigenous communities in Brazil. However, studies evaluating its toxicity and antioxidant action in vivo are scarce. In this sense, we propose to evaluate the toxicity and antioxidant potential of geopropolis from *Melipona orbignyi* (EGMO) and *Melipona quadrifasciata anthidioides* (EGMQ) bees in the *Caenorhabditis elegans* model. For this, the extracts were obtained from the extraction of geopropolis in ethanol/water 70% (w/v), during 24h at room temperature. Wild animals (strain N2) were maintained in NGM and E. coli (OP50-1) medium at 20 ℃. In the toxicity assay, ten animals in stage L4 were kept in different extract concentrations (12.5 – 250 µg/mL) during 24 and 48h. To verify the antioxidant action, the animals were incubated (24h) with the oxidizing agent 5-hydroxyl-1,4-naphthoquinone (Juglone, 80 µM). At the end of the tests, the number of live nematodes was determined. Our results show that both geopropolis extracts did not promote significant toxicity in all concentrations and periods evaluated. Regarding the death promoted by the pro-oxidant agent juglone, we observed an increase in the survival of 25.6 and 53.3% of the nematodes treated with the concentrations of 200 and 250 µg/mL of EGMO and 38% in the concentration of 250 µg/mL of the EGMQ. In summary, the data show the antioxidant action of geopropolis from *Melipona orbignyi* and *Melipona quadrifasciata anthidioides*, opening perspectives for future studies in the control of oxidative stress.

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14. CDC-48 influences SKN-1 activity in response to pathogen infection

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In Caenorhabditis elegans, bacterial infections produce an imbalance in the amount of ROS in the cell, causing oxidative damage in molecules. Attempts to counteract the damage occur by transcriptional activation of detoxification programs in response to high levels of oxidative stress. In our lab, we observe the effects of infection on the host by exposing C. elegans to the human pathogens Enterococcus faecalis and/or Pseudomonas aeruginosa, which are ingested and colonize the lumen of the intestine.
The infection triggers the expression of the transcription factor SKN-1, a protein that is activated by ROS and is involved in the activation of detoxification genes such as *gst-4* (glutathione Stransferase 4) and *gcs-1* (glutamate-cysteine ligase), which encode proteins that promote the survival of the animal. An RNAi screen looking for genes whose loss prevented SKN-1 activation on pathogens discovered cdc-48. CDC-48 is involved in targeting ubiquitinated substrates for proteolysis and helps maintain cellular proteostasis. Specifically, loss of cdc-48 by RNAi failed to cause the activation of SKN-1 reporter genes following infection with *E. faecalis* or *P. aeruginosa*. Congruently, the levels of SKN-1 in the nucleus were observed to be significantly decreased. Additionally, the absence of cdc-48 during infection renders *C. elegans* significantly more susceptible to the pathogen. My current focus is to understand the mechanism by which CDC-48 influences SKN-1 and this is an active area of ongoing investigation. In conclusion, CDC-48 affects the activation and nuclear localization of SKN-1 to affect survival on human pathogens such as *E. faecalis* and *P. aeruginosa*.
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15. Neural control of feeding by malonyl-CoA using *Caenorhabditis elegans* as a model system

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Obesity is an increasingly serious problem worldwide, and the few drugs available to treat and prevent the disease have severe side effects. Therefore, it is of great interest to elucidate the mechanisms that control appetite and body weight, to develop new therapies.
In mammals, changes in hypothalamic malonyl-CoA concentration have been postulated to contribute to regulation of appetite control. To determine if a similar behavior occurs in worms, we modified malonyl-CoA concentration using the mycotoxin cerulenin or RNAi knockdowns. Malonyl-CoA is a precursor of fatty acid biosynthesis, so the inhibition of Fatty Acid Synthase (FAS) increases its concentration. Cerulenin binds covalently to a cysteine residue in the active site of the eukaryotic FAS I ketoacyl synthase domain, blocking the interaction of the enzyme with malonyl-CoA. We have shown that cerulenin affects the development of *C. elegans*, causing the arrest of the worms in early larval stages. To determine if the feeding behavior of the worms responds to concentrations of malonyl-CoA, we evaluated their rate of food intake by measuring the pharyngeal pumping of young adult worms treated with different concentrations of the mycotoxin. In all cases we observed lower rates of pharyngeal pumping in treated worms than in untreated ones. Furthermore, RNAi assays to block neuronal FAS I expression showed a similar decrease in pump rates.
These results suggest that an increase in neuronal malonyl-CoA leads to a decreased feeding rate, indicating that this nematode could be a valuable model to contribute to the understanding of homologous processes in mammals.

16. The stress granule nucleator protein TIAR-1 is required for RNAi efficiency in the nematode germline

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Biomolecular condensates are made of proteins and RNAs that associate or dissociate depending on the cell requirements. The nematode gonad contains tissue-specific molecular condensates known as germ granules, which consist of P granules, Z granules, and foci mutator foci. Also in the gonad there are other types of biomolecular condensates that are not specific to this tissue, like P bodies and stress granules. P bodies are granules that are always present in the cells and are sites for mRNA storage or degradation. Stress granules are structures that are formed under harsh conditions and are usually formed when mRNA translation is arrested. The composition and function of these biomolecular condensates are not yet clear. Recently, several works link these biomolecular condensates with RNA silencing. In this project, we are studying the connection between the different germline RNA granules and exogenous RNA interference. TIAR-1 is an RNA binding protein that is required for stress granules formation. We have observed that in the absence of TIAR-1 the efficiency is affected. Currently, we are testing other RNA granule nucleators with the RNAi efficiency.

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17. The helicase CHD-7 regulates dauer entry and morphogenesis

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Dauers are long-lived larvae specialized in survival and dispersal that are induced when *C. elegans* encounters harsh environmental conditions in early development. The diapause entry implies an indefinite delay of reproductive fates and is followed by massive tissue remodeling, constituting a great model to study phenotypic plasticity. Previously, in a RNAi screen looking for dauer suppressors, we identified the chromodomain helicase CHD-7. Loss of *chd-7* completely bypass dauer development or fails to complete morphogenesis, resulting in partial dauers. Epistasis analysis placed CHD-7 in the TGF-b/DAF-7 pathway but also regulating the TGF- b/DBL-1 pathway, functioning as a TGF- b pleiotropic regulator. RNA-seq analysis of partial dauers developed from *chd-7* mutants, show 84 DEGs (Differential Expressed Genes) when compared to normal dauers. Among them, there is high representation of GPCRs (G-protein coupled receptors), collagens and transcription factors. As CHD-7 binds to chromatin for epigenetic regulation, we aimed to characterize CHD-7 targets necessary for dauer development. Thus, we conducted a RNAi-based screen to identify CHD-7 functional targets using RNAi-hypersensitive strains. In this work we will present novel candidate genes required for dauer development and morphogenesis.

Funding: Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)

18. Assessment of Paclitaxel toxicity in the model organism *Caenorhabditis elegans*

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Paclitaxel is a plant alkaloid extracted from the bark of the Pacific yew tree. This agent works by disrupting the microtubular network essential for cell division and other normal cell functions, ultimately causing cell death. These properties determine its therapeutic uses as an antitumor drug and the need for toxicity assessment. In this study, the round-worm Caenorhabditis elegans was selected as an experimental model to evaluate paclitaxel in a solution. Two exposure times: 1 h and 24 h, and 3 concentrations: 100 ng/ml, 500 ng/ml, and 1000 ng/ml, in addition to the control group and vehicle (DMSO), were assessed in liquid medium in triplicate in a total of four independent samples. Lethality, size (length and area), and locomotion were evaluated in adult (larval stage L4) N2 (wild type) worms. The results evidenced a 100% survival for all doses and exposure times. Interestingly, a dose-dependent effect was seen in the worm's size and locomotor parameters provided by the Microtracker device (Phylumtech S.A.) such as average speed and distance travelled. The results demonstrate the sensitivity of the invertebrate *C. elegans* to detect subtle effects in the nanosafety evaluation of therapeutic agents. These tests represent the basic parameters to be used for the nanosafety evaluation of different Paclitaxel nanoformulations currently being studied.
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19. Innexin contribution on the visual system of *C. elegans*

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Gap junction communication (GJC) allows cell-to-cell connection between adjacent cells in all multicellular organisms. *C. elegans* expresses 25 family members of GJC-forming proteins called innexins, expressed broadly. Whereas in the vertebrate visual system GJC mediate electrical synapses and shape light integration, innexin contribution on nematode light transduction is unknown. *C. elegans* can detect visible light and discriminate colors through LITE-1 receptors, decreasing pumping while increasing locomotion response. This escape behavior can be replicated using pyocyanin, a *Pseudomonas aeruginosa* derivative pigment, mixed with *E. coli* OP50. Pyocyanin induces a light dependent escape response in the presence of food. Innexin-mediated chemical transmission between neurons of the anterior visual circuit has not been studied. Using data from single cell RNAseq (CeNGEN), we chose 3 innexins expressed in ASJ, AWB, ASK, ASH, ASI, AWC, and ADL neurons (> 2% cells): *inx-2, 14, and 19*. Mutants for these innexins were evaluated on their avoidance response to pyocyanin. Worms chose between *E. coli* OP50 lawns mixed or not with pyocyanin in both light and darkness. After 1 hour, a chemotaxis index was calculated [(#worms in pyocyanin – #worms in control lawn)/(total scored worms)]. Our results show that while *inx-14* mutants were still repulsed by pyocyanin, *inx-2* and *inx-19* mutants were insensitive to this pigment, suggesting that innexins contribute to the visual integration of *C. elegans*.
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20. Evaluation of lipid accumulation and lethality in *Caenorhabditis elegans* treated with the bark of the stem of *Campomonesia adamantium*

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Obesity is a worldwide disease related to several comorbidities such as cardiovascular disease, diabetes and cancer. The accumulation of body fat is one of the main markers of this disease. Whereas C *ampomonesia adamantium* has lipid and glycemic control properties, this study sought to investigate the potential of *C. adamantium* stem bark to regulate lipid accumulation in *C. elegans* , as well as its toxicity. For this, we used animals of the mutant strain VS20 submitted to different concentrations of the extract (250 and 500 µg/ ml), quantifying after 48 hours the accumulation of body lipids by *oil red* . Animals of the N2 strain were treated with different concentrations of the extract (100-2000 µg/ mL) for 24 and 48 hours for toxicity assessment, with final viability assessment by reaction to touch with the platinum loop. The results show that the extract reduced the accumulation of body lipids compared to Vs20 control animals by approximately 43 and 50% at the two evaluated concentrations, respectively. There were no signs of lethality up to the highest concentration evaluated, in which the viability of 92% of the animals was maintained. In summary, the data show that the aqueous extract of the stem bark of *Campomonesia adamantium* is capable of reducing the accumulation of lipids, without showing toxicity and, therefore, encourages future studies related to its application in the control of obesity.

21. Effect of Dehydroepiandrosterone on hypoxia-associated damage in *Caenorhabditis elegans* GABAergic neurotransmission system.

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We postulate that the GABAergic system is especially sensitive to Hypoxia. Furthermore, drugs such as the neurosteroid Dehydroepiandrosterone Sulfate (DHEAS) have shown beneficial effects in hypoxic processes in mammals, however, at the cellular level, its exact mechanism of action has yet to be fully elucidated. Here, we used a chemical hypoxia model through Sodium sulfite (SS) exposure in *Caenorhabditis elegans* (*C. elegans*), a nematode whose response to hypoxia involves pathways and cellular processes conserved in mammals. The aim of this work was determining the effect of DHEAS on damage to the GABAergic system associated with SS exposure in *C. elegans*. We established an untreated group (CTL), a SS-exposed group (SS) and a SS-exposed group with DHEAS (SS + DHEAS). Worms were subjected to

Nose touch response (Not Assay) and observed in Nomarski and epifluorescence microscopy. DHEAS decreased the severity of hypoxic injuries in the pharynx. Shrinkage response of Not Assay and the level of severe damage in GABAergic neurons were significantly less frequent in SS + DHEAS group than SS worms. Also, the enhanced nuclear localization of DAF-16 and consequently the overexpression of chaperone HSP-16.2 by hypoxia were significantly reduced in SS + DHEAS worms. As well, DHEAS increased the survival rate of worms exposed to hydrogen peroxide. These results suggest that hypoxia-caused damage over the GABAergic system was prevented at least partially by DHEAS, probably through non-genomic mechanisms that involve its antioxidant properties related to its chemical structure.

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22. Deciphering the actions of essential oils in *C. elegans* as novel tools for anthelmintic therapy

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Essential Oils (EOs), plant extracts and herbal preparations have been extensively applied for human and veterinary health; their active agents have been isolated and incorporated into many current pharmaceutical preparations. Our hypothesis is that EOs of aromatic plants used for aromatherapy or food additives include compounds with anthelmintic activity and we test it using *Caenorhabditis elegans* as a model of parasitic nematodes. We developed behavioral and molecular assays in wild-type and mutant worms lacking receptors involved in locomotion to identify the main compounds of EOs mediating anthelmintic activities and their pharmacological targets. We also explored the combination of current anthelmintics with EOs' active compounds as a strategy to reduce drug resistance. Our goal is to provide a powerful platform for discovery of new antiparasitic compounds. We found six different EOs that inhibit *C. elegans* locomotion and egg hatching with different potencies, indicating their anthelmintic capacity, and identified the main bioactive compounds and receptor targets. Through single-channel and whole-cell recordings from *C. elegans* muscle cultured cells we determined that *C. elegans* L-AChRs and GABA receptors are modulated by these compounds and revealed their molecular mechanisms. Our results propose EOs as sources of natural compounds with promising polypharmacological profiles for anthelmintic therapies, decipher the molecular basis of their actions, and provide information about the efficacy of drug combinations that emerge as strategies to reduce drug resistance in nematodes.

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23. Comparative analyses of the complete mitochondrial genomes of the two filarial worms *Wuchereria bancrofti* & *Brugia malayi* with *Caenorhabditis elegans*

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Wuchereria bancrofti and *Brugia malayi* are filarial worms belonging to the phylum Nematoda and cause lymphatic filariasis (LF) disease in humans. *W. bancrofti* and *B. malayi* are Wolbachia-dependent organisms while *C. elegans* is a free-living Wolbachia-independent nematode. To investigate the conserved regions, present in the mitochondrial genome of these organisms, the complete mitochondrial (mt) genomes of *W. bancrofti* and *B. malayi* having sizes 13,636 bp and 13,657 bp in length, respectively are compared with *C. elegans* (13794 bp). These mt genomes were similar to each other in respect of their size, and AT content and encode the same 12 PCGs (nad1–6, nad4L, cytb, cox1–3, and atp6). Complete mt genome alignment identified 13 conserved regions in each of the organisms with some of these regions unique only to one organism. Phylogenetic analysis using the mt genome showed a close relationship between *W. bancrofti* and *B. malayi* but showed a common early ancestor with the *C. elegans* emphasizing an early evolutionary divergence.

24. The metabotropic glutamate receptor homologs MGL-1 and MGL-2 are key for sensing nutritional status in *C. elegans*.

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The mechanisms that allow the nervous system (NS) to sense nutritional state and adapt animal behavior are poorly understood in most species. The simplicity of its NS and its known connectome make *C. elegans* a useful system to study these mechanisms. Results from our laboratory showed that inhibition of the tyraminergic neuron RIM during fasting, enhances serotonin release from other neurons when the animal reencounters food, allowing it to slow down locomotion and start feeding. Mutations in the GPCRs genes, *mgl-1* and *mgl-2*, expressed in two presynaptic interneurons to RIM have been reported to induce autophagy even in well-fed animals. Here, we performed behavioral assays on *mgl-1; mgl-2* double mutants. We found that these animals, even when well fed, show a significant decrease in locomotion when they find food similar to fasted wild-type animals. Moreover, when we exposed these mutants to GFP-expressing bacteria, the fluorescence in the intestine is higher than that of wild-type animals, suggesting a higher feeding rate. These initial results suggest that the metabotropic receptors MGL-1 and MGL-2 are key for satiation sensing. We propose, therefore, to determine what these satiety signals are and the neuronal circuits involved. Given that this behavioral plasticity modulated by the nutritional state is observed throughout the animal kingdom, and that several fundamental processes are highly conserved, these results may provide universally relevant information.

25. LIN-42 and KIN-20 proteins regulate the circadian clock in the nematode *C. elegans*

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Circadian rhythms are biological processes that display endogenous oscillations close to 24h in different variables. Circadian oscillations are regulated by a set of genes, called “clock genes”, which make up the central clock. This central clock is entrained by Zeitgebers (synchronizers), such as light and temperature cycles. The mechanism of circadian rhythms has been extensively studied in various organisms; here we use the powerful model organism *C. elegans* to uncover the general principles of clock regulation. The aim of this work is to decipher the molecular components of the clock, using a reporter system based on bioluminescence. In particular, we focus on the study of evolutionarily conserved circadian proteins (KIN-20 and LIN-42). We observed a lengthening of the endogenous period in mutant strains for the KIN-20 and LIN-42 proteins; in turn, when rescuing the mutations, the endogenous period returned to its normal values, close to 24h. Thanks to the application of the auxin-indicated degradation (AID) technique, we were able to observe that the LIN-42 and KIN-20 proteins regulate circadian rhythms specifically in neurons. In summary, we found that the LIN-42 and KIN-20 proteins are critical for establishing an adequate circadian period of the molecular circadian cycle in the adult nematode.
Funding: CONICET/ AGENCIA/ Universidad Nacional de Quilmes (UNQ)

26. The effect of one probiotic in a transgenic model of *C. elegans* as possible treatment to autoimmune diseases like rheumatoid arthritis

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Rheumatoid arthritis affects people all over the world of all ages, the main problem is that there is no cure, and the treatments currently available are not very efficient. With the present project, it has been aimed to find a new alternative to treat symptoms such as inflammation using probiotics. In addition, it has been evaluated the possible positive effect on the nematode *Caenorhabditis elegans*. For this purpose, two strains were selected according to their characteristics: BX 26 and DR1565, after which they were observed under the stethoscope and compared with the wild strain N2. The whole process has been carried out to maintain the strains: synchronization, transfer to NGM medium and an osmotic stress assay in pursuit of modifying the cuticle that has the principal compound is collagen and being able to relate with an inflammation model. For now, only preliminary results have been obtained such as the characterization of the transgenic strains, acquisition, and maintenance of some probiotics that have been standardized for the concentration tests necessaries for providing to the nematode. In conclusion, results have been obtained like the beginning point because it was required to continue with the tests, the better probiotic need to be found and furthermore established as an inflammation model that can be used for future investigation in many fields such as immunology.
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27. Saturated fatty acid toxicity in *Caenorhabditis elegans*: an approach to studying high-fat diet

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The western diet is characterized principally by its high content of saturated fat, and other habits that unchain diseases that stand out of frequency the vascular and metabolic diseases. Stearic acid (SA) is one of these diets' most representative fatty acids. This study aimed to evaluate the effect of increased SA intake on the life cycle and lipid metabolism in *C. elegans*; and the chlorogenic acid (CGA, food antioxidant) ability to counteract the SA effects. We found that SA reduces the body size, reproduction, fat storage, and fat content in the N2 strain, while CGA reverts these effects. Genes involved in these mechanisms were evaluated with mutants and RNAi studies. Transcription factors such as *hif-1*, *sbp-1*, and the lipids metabolism enzymes *atgl-1* and *hosl-1* were the most prominent.

28. *In vitro* screening for anthelmintic effect of active pharmaceutical ingredients

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In the anthelmintic research field, *Caenorhabditis elegans*, a free-living nematode, has been shown to be a promising model organism for molecules screening, which may increase the yield of future discoveries.The demand for food without pesticide residues, safer working conditions and the increase in cases of anthelmintic resistance opens a new pathway for sustainable alternatives in the control of helminthiases, such as essential oils. The aim of this work was to evaluate the effect of different essential oils (EO) on wild and drug-resistant strains of *C. elegans*. Nematicidal and hatchability assays were carried out. Worms and eggs were incubated in different range concentrations of EOs dissolved in dimethylsulfoxide (DMSO) and ultrapure water. DMSO was used as negative control and ivermectin 1 mcg.mL or albendazole 10 mcg.mL was used as positive control. Their survival was monitored after 24 h and 48 h and analyzed by using RStudio. The resistance ratio (RR) and morphological changes of the most effective EOs were also determined. Results showed that EOs were lethal to strains resistant to the nematicides levamisole, albendazole, and ivermectin. The EOs also decreased the number of viable eggs. Furthermore, EOs caused damage to *C. elegans* structure. Taken together, EOs may be considered new drugs against parasitic nematodes.
Funding: FAPUR, CNPq e CAPES.

29. Review: Implementation of CRISPR/CAS9 technology applied in *Caenorhabditis elegans* as a possible therapeutic option for Alzheimer's disease.

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More than 100 years since Alzheimer's disease (AD) was identified, an effective treatment has not yet been developed and, together with the social cost, this represents a serious challenge for the world's health systems. Only recently has a drug (Lecanemab) been approved, which still requires further study due to its side effects. Recent studies suggest gene editing technologies as an ideal option for dealing with neurodegenerative diseases. CRISPR/CAS9 is a technology with high potential and its study requires analysis in living organisms; for this reason, *C. elegans*, being a neurobiological model, represents an important option to obtain data quickly and efficiently. To determine, through a review of studies and publications based on the use of CRISPR/CAS9 implemented in *C. elegans*, therapeutic opportunities to halt or prevent the development and progression of AD. As indicators we have publications from 2019 to 2022 that propose and prove that CRISPR/CAS9 is a useful gene editing tool for AD in the *C elegans* model. Roshni M et al. represent one of the studies that best demonstrates the potential of CRISPR/CAS9 overexpressing genes that allow β-amyloid clearance in *C. elegans* CL2006. The importance of autophagy in AD is clear, as Hongru L et al. demonstrated in *C. elegans* CL2122C strains the accumulation of autophagosomal vacuoles leads to alterations in autophagy and motility processes. CRISPR/CAS9 could be used to regulate those genes responsible for mediating autophagy processes in order to prevent the accumulation of β-amyloid and even Tau

30. Evaluation of the effects of purine-disustitutes on the aggregation of α-synuclein in *Caenorhabditis elegans*

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Parkinson's disease (PD) is a progressive neurodegenerative pathology characterized by cognitive and motor impairments, associated with the degradation of dopaminergic neurons of the substantia nigra pars compacta caused by aggregation of α-synuclein protein (α-syn). Currently the disease is incurable and therapeutic strategies are focused on the symptoms, not able to reverse or slow disease progression. Recently the inhibition of α-syn aggregation has been considered as a potential pharmacological strategy. Based on this, Espinosa-Bustos et al. synthesized purine-disubstituted ligands directed to multiple targets that target Histamine 3 receptors and the C-terminal end of α-syn. In this study, three purine-disubstituted ligands (0; 2.5; 25 and 250 μM) are exposed *in vivo* in the transgenic animal model *Caenorhabditis elegans* NL5901, which expresses human α-syn in muscle cells, where synchronized L1 larval stage nematodes were exposed to compounds 3c, 3f and 3g for 72 hours from L1 stage. Among the ligands under study, 3f (250 μM) and 3g (250 μM) significantly reduced α-syn aggregation compared to the control, while 3g (250 μM) showed a significant increase in the motility phenotype. Furthermore, none of the three ligands demonstrated significant toxic effects at the concentrations used during the study. Therefore, the results suggest that 3g represents a potential candidate to reduce PD-associated α-syn aggregation. The ligands represent a good starting point for future studies to assess whether the exposure to such molecules can impact long-term α-syn aggregation (e.g., in older, sicker animals) as well as if they are capable of disaggregating α-syn previously formed.

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31. Evaluation of the antitumoral action of Uliginosin B in the *let-60* gain-of-function model in *Caenorhabditis elegans*

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Uliginosin B (ULI), a dimeric fluroglucinol, is present in several species of the genus *Hypericum*, and has demonstrated a possible anticarcinogenic action *in vitro*. Epidemiological data highlights cancer as the second disease with the highest death rate in the world. There is an increasing search for therapies with greater specificity and fewer adverse effects, based on plant-derived drugs. Therefore, the use of the nematode *Caenorhabditis elegans* has advantages of mutant strains that mimic mammalian diseases. In this study we used N2 (wild type) and MT4244 (*unc-24(*e138); *let-60*(n1046) IV) strains. Worms at the L1 stage were exposed to ULI (1, 5, 10 and 20 µM), with the control group exposed to 2.5% dimethylsulfoxide (DMSO). After 30 minutes exposure, the worms were washed and poured into Petri dishes with nematode growth medium (NGM) and *Escherichia coli OP50*. After 48 hours, the experimental tests were performed. ULI was safe for the MT4244 strain, with no significant mortality rate. In the longevity assay, a significant reduction was observed in the lifespan for both N2 and MT4244 strains. On the second day of adulthood, the worms only showed a delay in the development of the multivulva phenotype (muv) of the MT4244 strain, with significant reduction at the highest concentrations. Based on these results, it was possible to verify that the ULI may not have a protective action in the formation of the muv phenotype, but additional tests will be carried out.
Funding: CAPES and CNPq

32. Safety evaluation of ebselen nanoparticles co-encapsulated with ginger oil (Zingiber officinale) in *Caenorhabditis elegans* as a new possible Covid 19 therapy

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The pandemic caused by the SARS-CoV-2 started in December 2019, and until this moment has caused more than 6 million deaths worldwide. For that reason, the development of new drug therapies that are safe and efficient against the SARS-CoV-2 are a valid alternative. Ebselen, an organic chalcogen molecule, showed efficacy *in vitro* by interacting with the SARS-CoV-2's Mpro. On the other hand, its toxicity at some doses and poor solubility are factors that restrain its use. Then, the nanoencapsulation of ebselen in a nanostructure may be a valid strategy. Therefore, the objective of this research was to develop new ebselen polymeric nanoparticles and evaluate its safety and efficacy in *C. elegans*. The nanoparticles were developed using the polymer Eudragit® RS100 and the ginger oil as the particle nucleus and evaluated its physicochemical properties. The toxicological endpoints analyzed in the nematode were survival rate, brood size and body length using a concentration range of 1-200µM. Moreover, the antioxidant enzymes GST-4, SOD-3 and the transcription factor DAF-16 were also evaluated. Our results showed that the particles have 63 nm, a polydispersity of 1.3 and the pH of 6.2, which are suitable parameters for a nanometric system. The toxicity assays showed no alterations in any

parameters, moreover the particles modulate the expression and activity of the GST-4 and induce the migration of the DAF-16 to the nucleus. In conclusion, we have developed stable and safe polymeric nanoparticles loaded with ebselen, which were capable of modulating an important enzyme in the nematode antioxidant system.
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33. Starvation increases attraction to odorants through CRH-1/CRB activity in the nervous system and intestine

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To survive starvation, *Caenorhabditis elegans* has a diverse array of responses ranging from metabolic adaptation to behavioral changes, yet starvation also has long-term repercussions in the nematode, including delays in growth and alterations in development of neurons and the gonad, though its persisting consequences on behavior are poorly understood. Our data showed that adult worms subjected to starvation in the first larval stage exhibited an increase in attraction to the odorant 2-butanone that is dependent on the transcription factor *crh-1,* an ortholog of the cAMP response element-binding protein (CREB). Still, the downstream targets of CRH-1/CREB and the tissues where it is needed are unknown. In this work, through the usage of tissue-specific RNAi, we found that CRH-1/CREB is needed both in the intestine and nervous system to increase attraction to butanone after L1 starvation. Moreover, the activity of this transcription factor is only required during this insult and becomes dispensable during the recovery period. To infer the genomic targets of CRH-1/CREB during starvation, we implemented Chromatin Immunoprecipitation coupled to tagmentation and sequencing (ChIPmentation-seq) against the histone mark H3K27ac and prepared libraries from wild-type and *crh-1*-knockout worms, in feeding conditions or after starvation. The dual requirement of CRH-1/CREB in the intestine and nervous system suggests that in both tissues this transcription factor elicits transcriptional changes that lead to inter-tissue signaling, ultimately causing an increase in the attraction to 2-butanone. This hypothesis will be tested using the data generated with our ChIPmentation-seq experiments.
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34. Effects of aging on the germ cells responses to stress

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The *C. elegans* gonad is an excellent model to study aspects of cell biology because it is one of the biggest organs in the nematode and in conjunction with its transparency, it allows us to observe processes *in vivo*. Several responses to stress have been observed in the nematode gonad; among them, increased germ cell apoptosis, stress granules formation, changes in gonad morphology. Our aim is to study the effect that aging has on germ cell response to stress. In general, during aging, there is a delay in cellular functions, as well as a loss in the control of protein folding, loss of muscle functions, a reduction of metabolic functions along with others. Particularly, in the gonad has been observed mitotic and meiotic arrest, tissue deterioration and shrinking; therefore it is possible that the protective actions of the gonad in the face of stress peaks or prolonged stress must be affected. In this study, we began to explore how the gonads of five-day-old animals respond to stress by subjecting animals to a single heat shock exposure or by exposing adult animals to heat shock every day for 5 days. We observed that the combination of maturity and continuous stress did not affect nematode's ability to form stress granules. However, we observed a reduction in germ cell apoptosis, which can be explained by a meiotic progression arrest more than a failure to respond to stress. We will continue exploring the effect of stress in older animals.

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35. Intergenerational effects of high temperature-induced diapause

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Animal phenotypic plasticity is crucial to cope with environmental stress caused by human-induced climate change. *Caenorhabditis elegans* adapt to stressful conditions by entering diapause, forming the stress-resistant dauer larvae. Triggers of diapause include inanition, high temperatures (27°C), crowding, and exposure to bacterial pathogens. The latter requires exposure to pathogenic bacteria for two generations and can be inherited transgenerationally, representing a further adaptation to environmental challenges. We ask whether other environmental stresses, such as high temperature, can create a genetic memory that changes progeny behavior. Specifically: How does dauer entry by high temperature affect this decision in the next generations? Parental worms (P0) enter diapause at high temperatures (27°C) at a rate of ¼ of the population, and this penetrance duplicates to ½ in the F1 of hermaphrodites who diapause. In contrast, P0s who did not enter diapause at 27°C have progenies that enter dauer at a rate of ¼. We also show that exposure to the ascaroside Ascr#5, a component of pheromones, does not generate dauer entry differences in the generations following the maternal dauer experience. This study suggests that temperature could be a different inductor of diapause generating intergenerational but not transgenerational memory. We speculate that dauer passage by high temperature could affect the next generation's gene expression and sensory neuron activity

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36. Implementation of the aldehyde dehydrogenase (ALDH) activity assay in *Caenorhabditis elegans*

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Caenorhabditis elegans (*C. elegans*) is a model organism that has been used to study the effects of neurotoxicants, including rotenone and benomyl, both widely used in the agroindustry. The toxic mechanism behind these pesticides is ALDH inhibition, either directly (benomyl) or through the ALDH cofactor (rotenone). Considering the critical role of this enzyme in the detoxification of reactive aldehydes, the aim of this work was to set up an assay to determine ALDH activity in *C. elegans* to assess the consequences of rotenone or benomyl exposure. Wild-type nematodes in the L4 stage were exposed for one hour to either rotenone or benomyl at a final concentration of 10 uM. They were washed thereafter 3 times with M9 buffer, collected, and stored at -80 °C. On the day of the assay, the samples were defrosted and homogenized in 0.25 M sucrose/0.1 mM EDTA in a volume equivalent to 10% w/v of the nematode mass. ALDH activity was measured spectrophotometrically by following the production of NADH at 340 nm. The reaction was started by the addition of 0.1 ml of acetaldehyde and followed over a 10 min period. As expected, the results show that both rotenone and benomyl inhibited ALDH activity with respect to control animals (230 fold and 13 fold, respectively) demonstrating that this technique was sensitive enough to detect changes in ALDH enzymatic activity. Analysis in progress is evaluating compounds that can restore or enhance the enzyme activity.

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37. Geraniol improve impaired locomotion in *C. elegans* Parkinson's disease models

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Due to the increase in life expectancy worldwide, age-related disorders such as neurodegenerative diseases (NDs) have become more prevalent. Elevated levels of oxidative stress could modulate the progression of NDs. For example, in Parkinson's Disease (PD) it has been shown that compromising the capacity to scavenge free radicals can exacerbate α-synuclein (α-syn) aggregation and proteotoxic damage. Geraniol (GL), a plant-derived essential oil, has recognized antioxidant properties. Considering that oxidative stress contributes to proteotoxic disease progression, compounds with antioxidant activity have been postulated as potential therapeutic agents. *C. elegans* is widely used in biomedical research. There is a high level of homology between *C. elegans* and mammalian genes (including proteins involved in cytoprotective mechanisms). In fact, several NDs can be recapitulated in this animal. In this work, we use *C. elegans* PD models to evaluate the *in vivo* effects of GL. We found that GL improves impaired locomotion in PD worms. Interestingly, GL also decreases α-syn aggregation. These preliminary results indicate a potential anti-proteotoxic effect in *C. elegans* models of PD. Therefore, we propose to combine genetic, microscopy and behavioral techniques to unravel GL effect in *C. elegans* ND models. These studies could provide a proof of concept of the potential of GL as a promising compound to retard proteotoxic diseases.

38. SBP-1: a protein involved in cholesterol metabolism modulation by the endocannabinoid (eCB) 2- AG in *C. elegans*

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Cholesterol is an essential constituent of eukaryotes membranes and its derivate metabolites serve as signaling molecules that are crucial for growth, development, and differentiation. *C. elegans* requires exogenous cholesterol to survive and perturbations in cholesterol trafficking result in an early development larval arrest. Thus, tight regulation of the sterol storage and distribution within the organism is critical. Even though cholesterol interacts with multiple lipid species, very little is known about how lipids influence cholesterol trafficking. Recently, we have demonstrated that the eCB 2-Arachidonoylglycerol (2-AG) plays a key role in *C. elegans* through modulating sterol mobilization and it can rescue the larval arrest phenotype under cholesterol starvation. However, worms lacking the SREB (Sterol Regulatory element-binding protein) ortholog *sbp-1* remained insensitive to the 2-AG rescue in sterol-depleted medium. Also, SBP-1 silencing over *daf-2(e1370)* mutants increases dauer formation under normal cholesterol diet. Therefore, our results suggest that SBP-1 is involved in the 2-AG signal transduction pathway to mobilize cholesterol. In order to elucidate the molecular basis of this mechanism experiments are in progress to explore the genetic interaction of *sbp-1* with key genes involved in the synthesis of eCBs. Undoubtedly, unraveling the mechanistic basis of 2-AG-mediated cholesterol mobilization in *C. elegans* could have important implications for a greater understanding of human pathological conditions associated with impaired cholesterol homeostasis.
Funding: CONICET-IBR

39. Hydroethanolic extract of the stem bark of *Nectandra cuspidata* protect *Caenorhabditis elegans* from oxidative stress and heat stress

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Oxidative stress is a process in which there is an imbalance between the production of free radicals and the body's ability to neutralize them, leading to development of chronic illnesses. *Nectandra cuspidata* Nees (Lauraceae) has presented in reports described in the literature, potentially antioxidant compounds, such as alkaloids and sesquiterpenes. Therefore, the aim of this work was to investigate the *in vivo* antioxidant activity and protection against heat stress of the hydroethanolic extract of *N. cuspidata* bark (EHNC). To evaluate the *in vivo* antioxidant activity, the nematodes were pre-incubated with different EHNC concentrations (6.5 – 500 µg/ml) for 1h, and exposed to Juglone (40µM) for 24h at 20ºC. To evaluate the resistance to heat stress, nematodes were induced by increasing the culture temperature from 20 to 37 ºC over a 6h period, then were kept at 20ºC to recover. The animals were considered dead when they did not respond to the stimulus with a platinum wire. The average of three independent assays was obtained. The oxidative stress induced by Juglone reduced the animals viability to 42%. The treatment with EHNC increased animal survival by 42% (50 µg/ml) and 79% in the highest concentration (500 µg/ml). A protective effect of EHNC on nematode survival was observed in all evaluated concentrations after a maximum period of 6h. Taken together, these data open new perspectives for the investigation of a safe natural product with properties to prevent oxidative damage and resist thermal stress.
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40. The identification of intergenerational diapause-inducing bacteria from complex natural ecosystems.

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The state of diapause is a strategy used by many species to escape stress. For example, nematodes enter diapause as a defense mechanism against bacterial pathogens, a response that requires the RNAi machinery from hosts and sRNAs from the bacteria. These studies however, were done with laboratory-reared human pathogens but the impact of natural microbiota on diapause entry has not been studied. To address this question, we isolated a consortium of bacteria from the soil and fed them to *C. elegans* expressing a dauer specific fluorescent marker (*col-183::mCherry*). The mix of soil bacteria induced diapause in the second generation at a 5% rate, similar to pathogens and starvation. We isolated each bacterium from the consortium and sequenced their 16S ribosomal RNA, identifying them as *Comamonas koreensis, Chryseobacterium indologenes, Stenotrophomonas tumulicola,* and *Rhodococcus qingshegii.* Animals developed normally and did not avoid bacterial lawns. Dauer formation was only observed in the second generation of animals feeding on *R. qingshegii,* being 17% at 20°C and 29% at 25°C. The presence of other bacteria in the consortia seem to dilute but not eliminate the effect of *R. qingshegii* on dauer formation. These results suggest that dauer entry may be a common strategy found in natural ecosystems not necessarily in response to starvation but rather to the microbiota composition of the soil. Whether this is a heritable response, remains to be tested in the future.
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41. Bacterial diets are able to modulate life-history treats in *C. elegans* models of neurodegenerative diseases

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As life expectancy increase, age-related disorders, such us neurodegenerative diseases (ND), have become more prevalent. Moreover, conventional treatments only attenuate some of the symptoms, but fail to arrest or delaycharacteristic neuronal proteotoxicity that characterizes them.. Thus, new challenges emerge to science in order to understand molecular basis of these disorders. Lately, the gut-brain axis has gain attention and a close relation between gut microorganism and ND has been proposed. In this context,T the aim of our work was to evaluate the relevance of the microbiota in the development and progression of proteotoxic-based disorders, assessing the impact of six non-pathogenic bacterial diets on life-history traits in *C. elegans* models of neurodegenerative disordersND (vs standard OP50). In a first approach, we found 2 bacteria, *Escherichia coli* K12 and *E. coli* HB101, able to improve locomotion in liquid media, in worm's model of Parkinson disease (PD) at adult day 4, versus the traditional *E. coli* OP50. Moreover, an age-dependent locomotion improvement, between larva- L4 and adult day 4, was observed in solid media after feeding PD model´s worms with 4 different bacteria versus *E. coli* OP50. We also On the other hand, we obobserved an increase thatin the developmental timing of wild-type worms was increase when animals were grown in 4 bacteria versus *E. coli* OP50, but more interesting was the accelerated developmental rate selectively found in models of PD and Huntington disease feed with *E. coli* BL21 (DE3). We are currently evaluating aggregate numbers, lifespan and mitochondrial morphology among others. Our

results allowed us to identify bacteria with the ability to drive physiological outcomes and improve health status of *C. elegans* models of neurodegenerative diseases.

42. Spatio-temporal expression analysis of genes involved in the electron transport chain of Caenorhabditis elegans using machine learning.

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The electron transport chain is a key process in cellular energy production and is vital for the proper functioning of all organisms. In the nematode *C. elegans*, the genes involved in this process have been well characterized, but there is still much to learn about genes associated with of this process. In this study, we used a supervised machine learning approach to predict new genes associated with the electron transport chain in *C. elegans* using a RNA-seq dataset that includes single cell expression of the first three divisions of the development, 502 distinct cell lineages and 410 terminal cell types, and whole animal transcripts at each stage of the life cycle. We found that our approach was able to identify several new genes that were previously unknown to be involved in this process. These findings have significant implications for our understanding of the genetic regulation of the electron transport chain.

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