16th PhD meeting

TECSBI

2024

BOOK OF ABSTRACTS

16-18 **SETTEMBRE** UNIVERSITY OF **MILANO-BICOCCA**

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

BtBs Department of Biotechnology and Biosciences

SCUOLA DI DOTTORATO BICOCCA

TeCSBi PhD TECNOLOGIE CONVERGENTI PER I SISTEMI BIOMOLECOLARI

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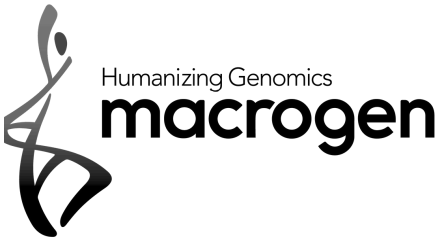

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16th PhD Meeting - 16/18 September 2024
UNIVERSITY OF MILANO-BICOCCA
Piazza dell'Ateneo Nuovo, 1 - 20126, Milano

PROGRAM

Lunedì 16 - Aula Sironi

9.00-9.10 Opening Day 1

9.10-9.30 **s1. Rosa Ranalli**
Urban pollinators in Italy: linking green areas with functional biodiversity for urban planning and management

9.30-9.50 **s2. Giuseppe Silvestri**
Exploring thermodynamic properties of biologically relevant macromolecular systems through free energy calculations: two case studies on the bench

9.50-10.10 **s3. Giulia Ghisleni**
The Heritage of the Deep Host-Microbiota Evolutionary Alliance: the Role of Micro-Biodiversity in Urban Contexts

10.10-10.30 **s4. Pietro Butti**
Microbial bioprocesses and synthetic biology for fostering circularity in the textile industry

10.30-11.30 Coffee Break + Poster Session 1

11.30-11.50 **s5. Alessia Metallo**
Modulation of Intracellular Ca2+ Dynamics and Proliferation by ISTAROXIME in Pulmonary Artery Smooth Muscle Cells

11.50-12.10 **s6. Stefano Bianchini**
Anticancer properties of Gratiola officinalis extract

12.10-12.30 **s7. Giorgia Ruotolo**
From Fibroblasts to Neurons. A journey to discover Joubert Syndrome.

12.30-12.50 **s8. Chiara Florindi**
Unveiling the biophysical mechanism of cardiomyocyte excitation-contraction coupling modulation by a membrane-targeted photoswitch

12.50-14.10 Lunch Break

14.10-15.00 **is1. Prof. Francesco Iorio**
Human Technopole
CRISPR-based second-generation of genetic-vulnerability-maps in cancer cells

15.00-15.20 **s9. Chiara Frigerio**
Exploring the interconnections between Fe-S cluster biogenesis and the DNA damage response

15.20-15.40 **s10. Francesco Abbiati**
GSL extract supplementation at the onset of yeast chronological aging imposes a metabolic remodelling that favours longevity

15.40-16.00 **s11. Roberta Pensotti**
A journey through Caenorhabditis elegans aging: insights in the implication of Ferroptosis

16.00-16.30 Coffee Break

16.30-16.50 **s12. Beatrice Negrini**
A multidisciplinary approach for the safe and sustainable design of novel nano-enabled antimicrobial products

16.50-17.10 **s13. Sara Fumagalli**
From Bioinformatics Tool Development to Microbial Transmission Analysis: Key Findings from Human and Environmental Microbiomes

17.10-17.30 **s14. Laura Beretta** *
Illuminating Protein-DNA interactions: using FID Assays to unmask true Protein-DNA Inhibitors in a Drug Discovery Campaign

17.30-17.50 **s15. Mirko Zago** *
Biocatalytic prepation of esters

Martedì 17 - Aula Sironi

9.00-9.10 Opening Day 2

9.10-9.30 **s16. Marco Barreca**
Tumour ecosystem dynamics in clinical triple-negative breast cancer depend on the chemotherapy regimen

09.30-09.50 **s17. Serena Seminara**
Effect of the inhibition of the Wiskott-Aldrich syndrome protein in the functions of microglia during neurodevelopment

9.50-10.10 **s18. Chiara Baioni**
Characterization of a CAFs model based on TGFβ treatment of NIH3T3 cells: which phenotypes are acquired and how long are they maintained?

10.10-10.30 **s19. Maddalena Bracchi**
Design of a 3D bioprinted meniscal scaffold based on ECM meniscal features

10.30-11.30 Coffee Break + Poster Session 2

11.30-11.50 **s20. Miriam Kuku Afanga**
Identification of miRNA-based biomarkers predictive of lung cancer treatment response and mechanisms involved in lung cancer progression

11.50-12.10 **s21. Giulia De Simone**
Unveiling nutrimetabolomic trajectories in elderly: hippuric acid and food-derived markers in frailty

12.10-12.30 **s22. Elisa Dama**
A machine learning approach to discover new biomarkers for lung cancer early detection and risk assessment

12.30-12.50 **s23. Serena Petrella**
New therapeutic targets in Mucinous Ovarian Cancer

12.50-14.10 Lunch Break

14.10-15.00 **is2. Stefano Diciotti**
UNIBO

15.00-15.20 **s24. Tommaso Sassi**
Development of an Escherichia coli cell-factory for the industrial production of 5-methylpyrazine-2-carboxylic acid

15.20-15.40 **s25. Alessandro Marchetti**
Salt-tolerant xylanases from a halotolerant bacterium isolated from Greek coastal environments

15.40-16.00 **s26. Vittorio Senatore**
Yeast fermentation for the upcycling of PET monomers

16.00-16.30 Coffee Break

16.30-16.50 **s27. Marina Meroni**
Induction of adipocytic differentiation in myxoid liposarcoma: new approaches to improve the effectiveness of the available therapies

16.50-17.10 **s28. Maria Chiara Barbera**
Targeting miR-29 to modulate the epigenetic clock: a novel strategy to counteract prostate cancer progression.

17.10-17.30 **s29. Alice Italia** *
Study on the impact of Toll-like Receptor 4 (TLR4) modulation in rare inflammatory-fibrotic diseases

18.00-20.00 Social event @BIM
Viale dell'Innovazione 3, Milano
with Non é la Zebra

non è la zebra

Mercoledì 18 - aula U3-05

9.00-9.10 Opening Day 3

9.10-9.30 **s30. Filippo Testa**
A new approach for direct visualization of unlabeled lipid nanoparticles for intracellular pathway analysis

9.30-9.50 **s31. Angela Maria Giada Giovenale**
A look at neurogenesis in Smith-Magenis syndrome: what goes wrong?

9.50-10.50 Coffee Break + Poster Session 3

10.50-11.10 **s32. Alessia Lambiase**
Exploring anti-aging and neuroprotective properties of plant extracts and their bioactive compounds in eukaryotic models of Parkinson's disease

11.10-11.30 **s33. Barbara Zerbato**
Targeting Hexosamine Biosynthetic Pathway to Overcome Resistance in Pancreatic Cancer Treatment

11.30-11.50 **s34. Elisa Toini**
Applying phylogenetic methods to identify plants with high drug discovery potential

11.50-13.10 **is3. Marco Nobile, Chiara Gallese**
UniVe & UniTo
Beyond the black-box: A practical guide to technical interpretability
&
The AI Act and the right to technical interpretability

13.10 Closing Remarks and Prizes

COLOR CODE

Industrial Biotech **Health and Biodiversity** **Biomedical and Health**

* To attend these sessions, participants are required to sign a confidentiality agreement to ensure that all research presented remains protected and is not shared without authorization

POSTER SESSIONS

Lun 16, 10.30-11.30 Poster Session 1

p1. Alice Armanni
Mapping the microbiome of hospitals and patients for solutions in risk monitoring

p2. Beatrice Colombo
Wild bees adaptation to anthropogenic habitats: a multi-Omic approach to implement innovative conservation and ecological transition strategies

p3. Lidia Favaretto
Tools of industrial ecology for the sustainability assessment of Nature-based Solutions

p4. Susanna Perotti
Enhancement of microbial biodiversity to promote environmental and human health

Mar 17, 10.30-11.30 Poster Session 2

p5. Martina Dramis
Engineering microbial cell factories for biomanufacturing chemicals and modified natural polymers suited for the formulation of high performance elastomeric nano compounds

p6. Mirko Frigerio Verga
Biotechnological approaches to support sustainable agriculture

p7. Gergő Borka
Development of Organ-on-Chip Based Methodologies for in Vitro Novel Compound Testing

p8. Maria Rita Chelazzi
Investigating the role of the SOWAHC-DIAPH1 complex in physiology and cancer

p9. Edvige Vulcano
Preliminary data of ICV delivery of human Neural Stem Cells in a mouse model of ALS

Mer 18, 9.50-10.50 Poster Session 3

p10. Flavio Corallo
Exploring the function of the CST complex at DNA double-strand breaks

p11. Francesca Misitano
Interaction between myofilament and SERCA2a activators on heart muscle mechanics

p12. Francesco Lapi
Multi-omics data analysis to characterize sex-specific metabolic shifts during embryo development

p13. Lorenzo Taglietti
Synthesis, Conformational Analysis and Preliminary Biological Evaluation of Iminosugar-based Pharmacological Chaperones for Mucopolysaccharidosis Type I

p14. Luca Moretti
Identification and characterization of anti-amyloidogenic natural compounds for the prevention of age-related neurodegenerative diseases

Speakers

s1. Health and Biodiversity

Rosa Ranalli
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Urban pollinators in Italy: linking green areas with functional biodiversity for urban planning and management

Rosa Ranalli[1 2], Andrea Galimberti[1 2], Paolo Biella[1]

[1] Department of Biotechnology and Biosciences BtBs, University of Milano-Bicocca
[2] NBFC, National Biodiversity Future Center

ECOSYSTEM SERVICES, GREEN AREA MANAGEMENT, POLLINATORS, URBAN BIODIVERSITY

The research project (in Spoke 5, NBFC) aims to identify and evaluate which urban elements can serve as refuges for pollinators. Laboratory activities focused on morphological and molecular analyses for taxonomic identification. DNA-metabarcoding and pollen grain counting identified the plants visited by pollinators and the amount of pollen transported. Moreover, studies analysed green area management, assessing the impact of mowing and the availability of nesting resources. Experimental setups were established to enhance urban biodiversity, providing trophic and nesting resources at a multi-taxa level. Results allowed us to identify the most efficient morphological groups in pollination services and how they benefit from green management practices, including reduced lawn mowing, increased availability of wood in urban forests and trophic resources. Finally, two reviews established the state of the art on urban biodiversity and concrete actions to conserve and enhance it.

Giuseppe Silvestri
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Exploring thermodynamic properties of biologically relevant macromolecular systems through free energy calculations: two case studies on the bench

Giuseppe Silvestri[1], Federica Arrigoni[1], Luca Bertini[1], Giuseppe Zampella[1], Luca De Gioia[1], Jacopo Vertemara[1]

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HPC, MD SIMULATION, FREE ENERGY CALCULATION, REDOX POTENTIAL, ROTAXANE

By leveraging High Parallel Computing, free energy calculations can be carried out efficiently, precisely, and cost-effectively, streamlining experimental observations and allowing reliable predictions[1]. In this project advanced free energy calculation methodologies were used to investigate two systems of biological and chemical relevance. The first case study evaluated Non-Equilibrium Thermodynamic Integration protocols to estimate redox potential differences in nine C. Beijerinckii flavodoxin's variants, confirming the reliability of this tool for such prediction[2]. The second case study examined amide-based rotaxanes in different solvents to understand solvent-rotaxane interactions, crucial for developing new molecular materials for biological-based applications[3]. These studies underscore the potential of advanced computational methods to enhance our understanding of complex molecular systems, paving the way for future innovations in both biotechnology and materials science.

1. Annu. Rev. Biophys. 2023. 52:113–38
2. Molecules 2023. 28, 6016
3. Nat. Rev. Chem. 2024. 8, 8–29

Giulia Ghisleni
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The Heritage of the Deep Host-Microbiota Evolutionary Alliance: the Role of Micro-Biodiversity in Urban Contexts

Giulia Ghisleni[1], Sara Fumagalli[1], Alice Armanni[1], Antonia Bruno[1], Maurizio Casiraghi[1]
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BUILT ENVIRONMENT, MICROBIOME, URBAN REGENERATION, UNIVERSITY HEALTH, METAGENOMICS

Investigating the role of reduced microbiome biodiversity in the rise of non-communicable diseases is a recent evolutionary concern affecting urban areas globally[1 2]. Current urban renovation plans overlook microbial evaluations. To address this, we developed a microbiome framework through Citizen Science to characterize urban microbiomes.
The UniBiome project aims to evaluate the health of the University Milano-Bicocca and the Politecnico di Milano from a microbiome-centered perspective. Samples were collected from both outdoor and indoor spaces, as well as from the skin and stool of students. The university microbiome was analyzed using amplicon-based sequencing followed by bioinformatics analysis. By leveraging the functional diversity of bacteria, we will create guidelines for biologically informed urban renovations to enhance the well-being of both students and the ecosystem[3].

1. Benton, M. L., Abraham, A., LaBella, A. L., Abbot, P., Rokas, A., & Capra, J. A. (2021). Nature Reviews Genetics, https://doi.org/10.1038/s41576-020-00305-9
2. Sonnenburg, E. D., & Sonnenburg, J. L. (2019). Nature Reviews Microbiology, https://doi.org/10.1038/s41579-019-0191-8
3. Bruno A, Fumagalli S, Ghisleni G, Labra M. (2022). Microorganisms, https://doi.org/10.3390/microorganisms10122311

Pietro Butti
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Microbial bioprocesses and synthetic biology for fostering circularity in the textile industry

Pietro Butti[1], Marta Simonetti[2], John Morrissey[3], Paola Branduardi[1]

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[2] Cotonificio Albini S.p.A., Albino (Bergamo)
[3] School of Microbiology, University College Cork

NATURAL DYES, COTTON HYDROLYSIS, TEXTILE WASTE, UPCYCLING, YEAST FERMENTATIONS

The current fashion system is based on a linear economy model, therefore a transition to a more sustainable circular system in which waste is minimized and recycled back into new raw materials is strongly needed. In this work, we first developed and scaled up a protocol for the upcycling of cotton textile waste to bioproducts through enzymatic hydrolysis and fermentation, using lactic acid production as a proof of concept. In parallel, the yeast Kluyveromyces marxianus has been engineered for the production of violacein-related textile dyes, while combining metabolic engineering and synthetic biology to increase the fluxes towards tryptophan, their precursor. Finally, these two approaches have then been combined in a never previously described manner.

s5. Biomedical and Health

Alessia Metallo
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Modulation of Intracellular Ca2+ Dynamics and Proliferation by ISTAROXIME in Pulmonary Artery Smooth Muscle Cells

Alessia Metallo[1], V. D'Angeli[1], L. Volonterio[1], F. Scola[1], M. Arici[1], M. Rocchetti[1]
[1] Department of Biotechnology and Biosciences BtBs, University of Milano-Bicocca

PASMCS, ISTAROXIME, SERCA2A, SOCE, PROLIFERATION

Smooth muscle cells (SMCs) switch from contractile to proliferative states in response to vascular damage. Istaroxime, a promising agent for acute heart failure, stimulates SERCA2a and inhibits Na+/K+ ATPase (NKA). This project investigates istaroxime's effects on intracellular Ca2+ dynamics and proliferation of rat pulmonary artery SMCs (rPASMCs), aiming to explore its potential role in vascular diseases. Istaroxime acutely reduced NKA current increasing cytosolic Na+ and Ca2+ levels; opposite effects were detected in chronic condition. Moreover, selective SERCA2a stimulation by istaroxime metabolite did not alter Ca2+ levels, suggesting further mechanisms explaining chronic effects of the drug. Istaroxime significantly reduced store operated Ca2+ entry (SOCE) and blunted rPASMCs proliferation. Overall, this suggest that istaroxime modulates rPASMCs intracellular Ca2+ and proliferation through SOCE inhibition, making it a potential candidate for vascular disease treatment.

Stefano Bianchini
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Anticancer properties of Gratiola officinalis extract

Stefano Bianchini[1], Francesca Cristani[1], Flavia Guzzo[1], Federica Bovio[1], Matilde Forcella[1], Paola Fusi[1]
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COLORECTAL CANCER, PLANT EXTRACTS, GRATIOLA OFFICINALIS, NATURAL COMPOUNDS.

Colorectal carcinoma (CRC) is one of the most common types of cancer worldwide. To treat such a heterogeneous disease, many drugs have been developed over the years. However, their efficacy is variable, and their administration may be related to the insurgence of strong side effects, urging the need to find new, complementary approaches. Amongst these, natural compounds present in plants have emerged as promising candidates, having shown antiproliferative and antioxidant activities on cancer cells in vitro. Here, we report that the ethanol extract derived from Gratiola officinalis has an impact on the E705 CRC cell line, causing a reduction in the proliferation signalling, the induction of apoptosis, and the disruption of the glycolytic metabolism.

Giorgia Ruotolo
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From Fibroblasts to Neurons. A journey to discover Joubert Syndrome.

Giorgia Ruotolo[1 2], Daniela Ferrari[1], Jessica Rosati[2]

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[2] Cellular Reprogramming Unit, Fondazione IRCCS Casa Sollievo della Sofferenza

JOUBERT SYNDROME, PRIMARY CILIUM, HIPSCS, HINSCS

Joubert Syndrome is a rare neurodevelopmental disease characterized by defects on the cerebellar vermis and malformation of the brain stem. It's also defined as ciliopathy, because of constant alterations of the primary cilium[1].
The primary cilium plays several roles during neurodevelopment, such as balancing proliferation and differentiation or promoting neuronal migration[2] . The differentiation of iPSCs into neural stem cells and then into the three neural populations represents a robust model for the characterization of the disease whose onset occurs during early stages of neurogenesis.
Thus, we collected biopsies from two JS patients with mutations in AHI1 with which we characterized the primary cilium, then, after reprogramming to iPSCs, we studied it in a more context-specific population, the neural stem cells[3]. Here, we will be able to evaluate many of the pathological mechanisms that affect primary cilium during neurogenesis.

1. Dong Y, Zhang K, Yao H, Jia T, Wang J, Zhu D, et al. Clinical and genetic characteristics of 36 children with Joubert syndrome. Front Pediatr. 2023;11: 1102639.
2. Shimada IS, Badgandi H, Somatilaka BN, Mukhopadhyay S. Using Primary Neurosphere Cultures to Study Primary Cilia. J Vis Exp. 2017. doi:10.3791/55315
3. Rosati J, Ferrari D, Altieri F, Tardivo S, Ricciolini C, Fusilli C, et al. Establishment of stable iPS-derived human neural stem cell lines suitable for cell therapies. Cell Death Dis. 2018;9: 937.

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Unveiling the biophysical mechanism of cardiomyocyte excitation-contraction coupling modulation by a membrane-targeted photoswitch

Chiara Florindi[1 2], Vito Vurro[2], Ludovica Cestariolo[1 3], Chiara Bertarelli[3], Jose Felix Rodriguez Matas[3], Guglielmo Lanzani[2 4], Antonio Zaza[1], Francesco Lodola[1 2]

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[2] Center for Nano Science and Technology, IIT-Italian Institute of Technology
[3] Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano
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PHOTOCHROMIC MOLECULES, PHOTOSTIMULATION, CARDIAC ELECTROPHYSIOLOGY

The use of light to control cell activity is a promising approach in cardiac research due to its precision and minimal invasiveness. Ziapin2 (Z2), a new azobenzene compound, has shown potential for light-driven modulation of excitation-contraction coupling (ECC) in hiPS-CMs, yet its biophysical mechanism is not fully understood. To explore this, we conducted functional experiments in adult mouse myocytes (V-CMs) and integrated our data with a numerical model of murine action potential (AP) that accurately reproduces the alterations induced by Z2 photoisomerization. Our results identified a link between Z2-induced membrane thickness changes and light-generated APs, highlighting the critical role of stretch-activated ion channels (SACs). Pharmacological blockade and in silico analysis suggest that Ca2+ permeable SACs might be primarily responsible for this effect. These findings clarify Z2 mechanism of action and open new perspectives for its application in cardiac research.

s9. Biomedical and Health

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Exploring the interconnections between Fe-S cluster biogenesis and the DNA damage response

Chiara Frigerio[1], Michela Galli[1], Sara Castelli[1], Diego Bonetti[1], Michela Clerici[1]

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SACCHAROMYCES CEREVISIAE, IRON-SULFUR CLUSTERS, DNA DAMAGE RESPONSE, REPLICATION STRESS

Iron-sulfur (Fe-S) clusters are protein cofactors that are present in several proteins among which we find factors involved in DNA replication, DNA repair, transcription and chromosomes segregation. This suggests a link between Fe-S clusters and genome stability. Biogenesis of Fe-S clusters involves many proteins (CIA proteins) that are conserved from yeast to humans, where mutations in Fe-S enzymes have been linked to several diseases and types of cancer. In Saccharomyces cerevisiae we have found that inactivation of specific CIA proteins causes synthetic lethality with the deletion of MEC1, the ortholog of human ATR. The kinase Mec1 plays crucial roles during the DNA damage response and during replication.
We are now exploring the molecular mechanisms underlying this synthetic lethality, in particular we are analysing the role of polymerases and nucleotides to better figure out how the CIA system can modulate the cellular response to DNA damage.

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GSL extract supplementation at the onset of yeast chronological aging imposes a metabolic remodelling that favours longevity

Francesco Abbiati[1], Ivan Orlandi[1], Marina Vai[1]
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GLUCOSINOLATES, AGING, SACCHAROMYCES CEREVISIAE, MITOCHONDRIA, GLUCONEOGENESIS

Glucosinolates (GSLs) are nitrogen- and sulfur-containing glycosides[1], produced as secondary metabolites by many plants. An extract rich in GSLs was obtained[2] from the seed-press cake derived as by-products of Camelina sativa oil extraction. We investigated GSL extract effects on aging process in the context of chronological aging, the established yeast model that simulates cellular aging of postmitotic quiescent mammalian cells[3]. We found that GSL supplementation at the onset of the chronological aging, namely at the diauxic shift, increases the chronological lifespan. This extension takes place in concert with a proper maintenance of mitochondrial functionality and a more efficient respiration. In addition, we found that GSL extract supplementation preserved TCA enzymatic activities and elicited an enhancement along the glyoxylate/gluconeogenesis axis resulting in a higher accumulation of trehalose, disaccharide fundamental for longevity in yeast.

1. Bravi, E.; Falcinelli, B.; Mallia, G.; Marconi, O.; Royo-Esnal, A.; Benincasa, P. Effect of Sprouting on the Phenolic Compounds, Glucosinolates, and Antioxidant Activity of Five Camelina sativa (L.) Crantz Cultivars. Antioxidants (Basel). 2023, 12, e1495, doi:10.3390/antiox12081495.
2. Pagliari, S.; Giustra, C.M.; Magoni, C.; Celano, R.; Fusi, P.; Forcella, M.; Sacco, G.; Panzeri, D.; Campone, L.; Labra, M. Optimization of ultrasound-assisted extraction of naturally occurring glucosinolates from by-products of Camelina sativa L. and their effect on human colorectal cancer cell line. Front. Nutr. 2022, 9, e901944, doi: 10.3389/fnut.2022.901944.
3. Orlandi, I.; Stamerra, G.; Vai, M. Altered expression of mitochondrial NAD+ carriers influences yeast chronological lifespan by modulating cytosolic and mitochondrial metabolism. Front. Genet. 2018, 9, e676, doi: 10.3389/fgene.2018.00676

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A journey through *Caenorhabditis elegans* aging: insights in the implication of Ferroptosis

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AGING, REDOX, FERROPTOSIS, CAENORHABDITIS ELEGANS

Life expectancy has greatly increased in the past few decades, with the growing risk of frailty as direct outcome[1]. A promising strategy to promote a healthier aging is targeting ferroptosis, a newly discovered mode of cell death that is caused by massive lipid-peroxidation mediated membrane damage, triggered by the accumulation of intracellular ROS and iron[2].
Here, the implication of ferroptosis in the aging process was investigated focusing the attention on redox homeostasis. The evaluation of C. elegans heat stress resistance, ROS levels and total glutathione amount showed a progressive disruption of redox balance over time. Moreover, gene expression analysis were carried out on differentially expressed genes induced by pro-longevity frataxin silencing and potentially involved in inhibiting ferroptosis[3]. Those genes were found to be downregulated during the worm's lifespan, suggesting a possible increment of ferroptosis in aging in a straight cross-talk with redox damage.

1. Yu, M., Zhang, H., Wang, B., Zhang, Y., Zheng, X., Shao, B., ... & Jin, K. (2021). Key signaling pathways in aging and potential interventions for healthy aging. Cells, 10(3), 660.
2. Larrick, J. W., Larrick, J. W., & Mendelsohn, A. R. (2020). Contribution of ferroptosis to aging and frailty. Rejuvenation Research, 23(5), 434-438.
3. Schiavi, A., Salveridou, E., Brinkmann, V., Shaik, A., Menzel, R., Kalyanasundaram, S., ... & Ventura, N. (2023). Mitochondria hormesis delays aging and associated diseases in Caenorhabditis elegans impacting on key ferroptosis players. Iscience, 26(4).

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A multidisciplinary approach for the safe and sustainable design of novel nano-enabled antimicrobial products

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NANO-ANTIMICROBIALS, SSBD, NANNANO-ANTIMICROBIALS, SSBD, NANOTOXICOLOGY, D. RERIO, KERATINOCYTES, LIFE CYCLE ASSESSMENTOTOXICOLOGY, D. RERIO, KERATINOCYTES, LIFE CYCLE ASSESSMENT

Nanoparticles-enabled products (NEPs) emerged as alternative antimicrobial agents but require early safety and sustainability evaluation. This work integrated nano-(eco)toxicology in vivo and in vitro studies and environmental impacts analyses of CuO NPs-engineered water filtration membranes as case study. D. rerio was exploited as model for developmental screening, while keratinocytes cell model was used to investigate human skin sensitization and irritation. The environmental impacts of the membranes' production were evaluated with Life Cycle Assessment (LCA) methodology. In vivo results showed a delayed hatching and development, while first in vitro outcomes suggest skin sensitization. LCA identified NPs content and electricity as main contributors to environmental impacts. The integration of nano-toxicology and LCA assessments represents a potentially effective methodology to provide a comprehensive framework to support decision-making at design stage for safe and sustainable NEPs.

1. Mantecca P. et al., 2015. Toxicological sciences. https://doi.org/10.1093/toxsci/kfv067
2. European Commission. 2020. https://ec.europa.eu/environment/strategy/chemicals-strategy_en
3. Vincent M. et al., 2018. Journal of Applied Microbiology. https://doi.org/10.1111/jam.13681
4. Bondarenko O. et al., 2013. Archives of Toxicology. doi:10.1007/s00204-013-1079-4

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From Bioinformatics Tool Development to Microbial Transmission Analysis: Key Findings from Human and Environmental Microbiomes

Sara Fumagalli[1], Giulia Ghisleni[1], Alice Armanni[1], Antonia Bruno[1], Maurizio Casiraghi[1]
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MICROBIOME, BIOINFORMATICS TOOL, META-ANALYSIS, METADATA COLLECTION, MICROBIAL TRANSMISSION

Microbiome research recognized vast sequencing data as valuable resource, evolving into a data-driven discipline. However, compartmentalized data storage often hinders accessibility and reuse[1].
This study investigated urban environments and humans interactions from a microbiome perspective, addressing associated challenges. We developed MADAME, a bioinformatics tool to streamline (meta)data retrieval, and introduced a graphical version for broader accessibility. Using MADAME, we retrieved hospital environmental (meta) data to perform 15 projects meta-analysis, and updated SKIOME collection[2]. To address metadata standardization, we organized Data Hunters workshop, where 29 UniMiB students curated metadata from 379 SKIOME collection projects. Finally, we analyzed microbial transmission in 21 families across Europe.
In conclusion, our study advanced microbiome research by enhancing data accessibility and reusability, setting the stage for further exploration of human-environment interplay.

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Illuminating Protein-DNA interactions: using FID Assays to unmask true Protein-DNA Inhibitors in a Drug Discovery Campaign

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DRUG DISCOVERY, HIGH-THROUGHPUT SCREENING, FALSE-POSITIVE HITS, INTERCALATING COMPOUNDS, FID ASSAY

Nucleic acids, pivotal in modulating gene expression, are increasingly recognized as valuable drug targets. The Fluorescent Intercalator Displacement (FID) assay emerges as an efficient and practical method for identifying new nucleic acid-binding ligands and small molecules. This study innovatively utilizes FID to enhance the identification of true-positive hits by distinguishing compounds that inhibit through intercalation from those that do not. The tagless nature of FID, which requires no modification of DNA or small molecules, simplifies the evaluation process. Using TO-PRO as a fluorescent marker, this assay detects small molecule-DNA interactions, capitalizing on TO-PRO's fluorescence enhancement upon DNA binding.

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s15. Industrial Biotech

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Biocatalytic prepation of esters

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BULK CHEMICALS, LMW ESTERS, ETHYL ACETATE, BIOCATALYSIS, FERMENTATION, HEMIACETAL DEHYDROGENATION, ADH

Small esters, like ethyl acetate, are bulk chemicals produced in huge amounts with energy intensive procedures, starting from fossil feedstock. 45% of the global greenhouse gases emissions are caused by the production and use of all the products necessary for modern human life. If the world is to reach its climate goals, there is the need to leave underground a significant proportion of the fossil feedstock and minimize environmental impacts of chemical manufacturing. For these reasons a lot of efforts have been made to find novel routes for small esters production starting from renewable raw materials and exploiting low-impact manufacturing, such as microbial fermentation or enzymatic reactions. In this work we disclose a process for the production of esters at industrially viable yields occurring under mild conditions. The process occurs with a previously not disclosed kinetics, which allow energy and raw materials savings and thus potentially reduced costs.

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Tumour ecosystem dynamics in clinical triple-negative breast cancer depend on the chemotherapy regimen

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TNBC, BIOINFORMATICS, CHEMOTHERAPY, TUMOUR-MICROENVIRONMENT, PRECISION ONCOLOGY

Triple-negative breast cancer (TNBC) treatment traditionally relies on chemotherapy, increasingly paired with immune checkpoint inhibitors (ICIs) as the standard of care[1]. Distinct chemotherapeutic agents may differently impact both the tumour and its microenvironment (TME). Despite extensive studies in cancer models[2], data on clinical tumours are scarce.

We aimed to compare the early modulation of cancer pathways, immune-related features, and selected genes in TNBC patients undergoing various neoadjuvant chemotherapy regimens: doxorubicin/cyclophosphamide, nab-paclitaxel/carboplatin, nab-paclitaxel, or paclitaxel.

We quantified 82 cancer hallmark, immune, and TME gene-sets in each sample performing an enrichment analysis. Additionally, selected genes were similarly evaluated.

Our research could elucidate chemotherapy dynamic effects on tumour microenvironment and reveal potential chemotherapy candidates for optimal pairing with ICIs.

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s17. Biomedical and Health

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Effect of the inhibition of the Wiskott-Aldrich syndrome protein in the functions of microglia during neurodevelopment

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NEURODEVELOPMENT; HUMAN INDUCED PLURIPOTENT STEM CELLS; GENETIC RARE DISEASE; IMMUNODEFICIENCY

The Wiskott-Aldrich syndrome (WAS) is a rare disease caused by WAS mutations, leading to immunodeficiency. In 40% of WAS patients neurological complications are reported. We propose that neurological deficits are partly due to impaired myeloid-cell-mediated brain development and homeostasis. The WAS protein (WASp) is indeed expressed by microglia, key cells for neurodevelopment and neuroinflammation. To define WASp's role in brain, we inhibited the protein pharmacologically in microglia derived from human-induced pluripotent stem cells or in zebrafish embryos.
In presence of WASp inhibitors (Wiskostatin, CK-666), microglia: 1) reduced phagocytic activity and changed motility (by time-lapse confocal); reduced cytoskeletal filopodia (by fixed cell immunofluorescence). Zebrafish embryos with CK-666 had slower response to stimulation and accumulation of brain apoptotic bodies.
These findings suggest that microglia dysfunction contributes to WAS-related neurological symptoms.

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Characterization of a CAFs model based on TGFβ treatment of NIH3T3 cells: which phenotypes are acquired and how long are they maintained?

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CAFS, TGF-B, NIH3T3

Cancer-Associated Fibroblasts (CAFs) play a critical role in cancer pathogenesis and therapy resistance. For this reason, they are appealing targets for anticancer strategies. The development of such strategies requires CAFs preclinical models. The aim of this work was to develop and characterize a CAFs model based on NIH3T3 fibroblasts treatment with TGFβ, the main responsible for fibroblasts differentiation in cancer. Our studies disclosed that a 24h treatment with TGFβ induce in NIH3T3 cells some CAFs phenotypes that are maintained at least for 5 days after stimulus removal. Indeed, treated cells show a regulated expression of CAFs markers, they acquire a glycolysis-based highly energetic phenotype, and they modulate cancer cells growth. However, other CAFs phenotypes are not recapitulated, such as CAFs enhanced proliferation and migration in comparison to normal fibroblasts. So, activated cells obtained by our protocol can be used as a CAFs model as regards the observed phenotypes.

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Design of a 3D bioprinted meniscal scaffold based on ECM meniscal features

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BIOPRINTING, ECM, MENISCUS, HYDROGEL

Menisci are fibrocartilaginous cushions found in the knee joint which main function is weight distribution. Their extracellular matrix is highly hydrated and mainly composed of collagen and glycosaminoglycans. Taking a cross section, the external part is vascularized and has higher mechanical properties, the inner part is smoother and not vascularized. Meniscal injuries are very common, but regeneration is very hard. In this work, the meniscal extracellular matrices (ECM) from both pediatric and adult patients were compared to study the different signatures in physiological and damaged states. These results were then used to design preliminary gelatin and hyaluronic acid-based bioprintable hydrogels. These hydrogels were characterized from the chemical, mechanical and physical properties. Bioprinting tests were also performed using mesenchymal stem cells to verify the biocompatibility. These results confirm that these hydrogels can be used for in vitro meniscal regeneration.

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Identification of miRNA-based biomarkers predictive of lung cancer treatment response and mechanisms involved in lung cancer progression

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NON-SMALL-CELL LUNG CANCER, BIOMARKERS, MICRORNAS

Non-small-cell lung cancer (NSCLC) is the main cause of cancer-related deaths worldwide1. This is mainly due to the lack of diagnostic/prognostic biomarkers to improve early diagnosis and ameliorate treatment response2. Recently, microRNAs (miRNAs) were reported to contribute to cancer progression and therapy resistance in NSCLC3. Here, we propose to functionally map the whole miRNome involved in NSCLC progression and therapy resistance, by taking advantage of a lentiviral-based library overexpressing the human miRNome (N=2580) in relevant lung cancer experimental models. Our findings will also contribute to the identification of predictive miRNA-based biomarkers and molecular targets to aid the development of alternative therapeutic approaches in unresponsive lung cancer.

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s21. Biomedical and Health

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Unveiling nutrimetabolomic trajectories in elderly: hippuric acid and food-derived markers in frailty

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FRAILTY, HIPPURIC ACID, FOOD-INTAKE BIOMARKERS, NUTRIMETABOLOMICS, MASS SPECTROMETRY

Frailty is a geriatric syndrome characterized by the decline in the physiological functions of multiple organ systems. There is an unmet need for reliable biomarkers to identify populations at risk of developing frailty, to offer strategies for their better identification/management. Due to the established association between dietary patterns and risk of frailty, the identification/measurement of food-intake biomarkers (FIBs), molecules derived from food ingestion/metabolism, is crucial for an objective information on dietary habits and metabolism.
This work focuses on the assessment of the role of hippuric acid, a human-gut co-metabolite derived from the polyphenols 'intake, as a predictive hallmark of frailty and the determination of the role of FIBs tested individually and grouped into food categories in frailty development. These findings could provide valuable insights into dietary interventions that promote healthy aging and reduce the burden of frailty in the older population.

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A machine learning approach to discover new biomarkers for lung cancer early detection and risk assessment

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EARLY DIAGNOSIS, MIRNAS, LIQUID BIOPSY, LUNG CANCER RISK-MODEL

Our objective is the identification of circulating miRNAs (c-miRs) diagnostic for LC to complement LD-CT screening and limit LC burden (1.8 mil deaths per-yr[1]). We combined 3 public datasets (qRT-PCR, microarray) and identified 45 c-miRs differentially regulated between 150 LC and 136 controls (RankProd method[2]). We profiled 45 c-miRs in 2 European LD-CT screening cohorts (72 LC, 261 controls; qRT-PCR), and built a 9 c-miRs risk model, with AUC=0.78. With second-level machine learning algorithm, we then integrated the 9 c-miRs score (ddPCR) to radiological features (Brock model[3]) in a cohort of indeterminate nodules (39 LC and 45 benign, <30 mm) from Fred-Hutchinson center, reaching AUC=0.93 and NRI=0.69. We are now extending the US cohort for final validation.
The identified biomarkers could enhance the selection of at-risk population, and the workup of indeterminate nodules, thus reducing overtreatment, downstream costs, and facilitate LC screening large-scale implementation.

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s23. Biomedical and Health

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New therapeutic targets in Mucinous Ovarian Cancer

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OVARIAN CANCER - CRISPR/CAS9 - PLK1 - TARGET THERAPY

Epithelial ovarian cancer(EOC)is the second most common cause of death from gynaecological cancers[1].Mucinous ovarian carcinoma(mEOC),a subtype of EOC,has poor prognosis at advanced stages due to limited chemosensitivity[2].PLK1,a serine/threonine kinase,crucial for mitosis,G2/M checkpoint regulation, and cell survival.mEOC is sensitive to PLK1 inhibition,suggesting potential therapeutic target[3].Aim of this project is to identify, using CRISPR/Cas9 lentiviral libraries, new therapeutic targets, and genes in synthetic lethality with PLK1 inhibitor onvansertib.EFO27 cells were transduced with lentiCas9 plasmid to obtain the expression of Cas9 enzyme,then the screening was performed,with and without PLK1i.Bioinformatic analyses identified survival-related genes(ZC2HC1C,RPA2,KIN,TUBG1,SMC2, CDC26, CDC42,HOXA9,TAF10,SENP1,MRPS31,COPS2)and synthetic lethal genes with PLK1 treatment(JUND,CARD9,BCL2L2).The results were validated on different mEOC cell lines:EFO27,MCAS, TOV2414 and OCM.72

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Development of an *Escherichia coli* cell-factory for the industrial production of 5-methylpyrazine-2-carboxylic acid

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BIOREFINERY, METABOLIC ENGINEERING, EZYME ENGINEERING, FBA

On 25 November 2020, the European Union adopted the Pharmaceutical Strategy for Europe. This initiative highlights that the delocalization of basic and fine chemicals manufacturing outside the European Union has reached a critical point, where disruptions in the supply chains are no longer mitigated by local manufacturing. Therefore, a considerable effort is being invested to develop local, innovative and more environmentally friendly routes to existing chemicals. Thus, we are currently working on developing and optimizing and alternative strategy to produce the pharmaceutical building block 5-methylpyrazine-2-carboxylix acid (MPCA), currently used to produce antidiabetic drugs. The original concept was hindered several problems, such has the toxicity of the product, the short activity of the first enzyme and the high cost of the current substrate. Therefore, we devised different strategies to tackle these roadblocks to develop a fully implementable process.

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Salt-tolerant xylanases from a halotolerant bacterium isolated from Greek coastal environments

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EXTREMOPHILES, ENZYME DISCOVERY, HALOTOLERANCE, XYLANASES, DEGRADATION.

Mediterranean coasts are extreme habitats due to high salinity and nutrient scarcity. Halotolerant organisms living in these habitats can handle high salt concentrations. There, glycoside hydrolases (GHs) are pivotal in polysaccharides degradation. Here we report our studies on xylanases from Bacillus altitudinis CML04, a halotolerant bacterium isolated in Crete Island. This bacterium can grow on xylan as solely carbon source and enhance xylanolytic activity in presence of salinity stress. Genome mining analyses identified two different GHs, belonging to families 11 and 30, putatively secreted and involved in xylan degradation. These enzymes exhibit activity on xylan-based polysaccharides and moreover, can withstand salinity stress exceeding 2M. Future analyses will assess the degradation mechanisms and products, as well as the eventual effect of salt stress on their expression. This work will contribute to understand the role of halotolerant GHs in the degradation of polysaccharides.

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Yeast fermentation for the upcycling of PET monomers

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SACCHAROMYCES CEREVISIAE, POLYETHYLENE TEREPHTHALATE (PET), BIOCONVERSION, SYNTHETIC BIOLOGY, BIOPROCESS ENGINEERING

The majority of waste PET is landfilled, incinerated or dispersed in the environment; only about 30% is recycled; enzymatic recycling is an emerging strategy for PET depolymerization, releasing terephthalic acid (TPA) and ethylene glycol (EG). This work focuses on TPA and EG upcycling by yeast fermentation to produce protocatechuic acid and glycolic acid (GA), and on the use of EG as a carbon source.
For the bioconversion of TPA, several heterologous genes were introduced, including potential transporters.
A DoE approach was used to maximize GA production with S: cerevisiae; screening of non-Saccharomyces yeasts revealed Scheffersomyces stipitis as the best producer, obtaining 23.79 ± 1.19 g/L GA.
The role of YLL056C and GOR1 in EG catabolism was investigated in S. cerevisiae, in parallel with the expression of heterologous genes to improve the conversion of EG to GA.
Our research shows promising results and intriguing challenges in the upcycling of PET monomers by yeast fermentation.

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Induction of adipocytic differentiation in myxoid liposarcoma: new approaches to improve the effectiveness of the available therapies

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MYXOID LIPOSARCOMA, TRABECTEDIN, PIOGLITAZONE, RXR AGONISTS, ADIPOCYTIC DIFFERENTIATION

Myxoid liposarcoma (MLPS) is characterized by the expression of the FUS-DDIT3 fusion protein, which prevents terminal adipocytic differentiation[1]. Trabectedin is very effective in MLPS patients, but resistance mechanisms arise[2 3]. By ChIP-Seq analysis on MLPS sensitive and resistant patient derived xenografts (PDX)[4 5], we confirmed that the block of adipocytic differentiation is one of the resistance mechanisms and that the combination of trabectedin with the PPARγ agonist pioglitazone is able to restore adipocytic differentiation, overcoming resistance[6]. Since clinical trials are underway in MLPS patients[7], we evaluated possible pharmacokinetic interactions between the two drugs in PDXs and in the first four patients enrolled. Since PPARγ and RXR heterodimerize and the heterodimer is permissive[8], to further improve the efficacy of trabectedin and pioglitazone, we used the RXR agonist IRX4204. It led to a significant improvement in efficacy in both the sensitive and resistant PDXs.

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Targeting miR-29 to modulate the epigenetic clock: a novel strategy to counteract prostate cancer progression.

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AGING, PROSTATE CANCER, EPIGENETIC, CHROMATIN ORGANIZATION, MIRNA.

Epigenetic reprogramming has been recently established as an essential Hallmark of both cancer and aging[1 2]. Indeed, the aging process itself is the most prominent single risk factor for developing cancer[3].
We identified a core signature of epigenetic modifiers targeted by miR-29, a microRNA whose expression increases with age in healthy tissues and which, in contrast, is decreased in prostate cancer.
Inhibition of miR-29 leads to epigenetic rejuvenation, while its enhancement accelerates aging and impairs proliferation in the endocrine-resistant PC3 prostate cancer cell line.
Our findings uncover miR-29 as a major regulator of the aging process and reveal a possible application of RNA-based therapeutics in hindering cancer progression.

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Study on the impact of Toll-like Receptor 4 (TLR4) modulation in rare inflammatory-fibrotic diseases

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TLR4, RARE FIBROSIS, IN VITRO, ANTAGONISTS

The project focuses on the modulation of fibrotic phenotype up-set in rare diseases through a Toll-like Receptor 4 (TLR4) antagonist.
We evaluated the effect of TLR4 antagonist FP7 and FP12 on fibrotic up-set.
Fibrosis is an outcome of the repair response to tissue damage that if dysregulated leads to a pathological condition that can affect different organs and functions. It is known that inflammation plays a key role in the critical cellular process of fibroblast activation that leads to fibrosis up-set.
The recent discovery of complex crosstalk between fibrosis progression and inflammatory pathways underlines the central role of TRL4 and its potential as a new drug target. Here it is proposed an in vitro screening on cellular models of fibrosis with TLR4 antagonists to identify new potential drugs targeting Idiopathic Pulmonary Fibrosis (IPF) and intestinal fibrosis, a rare fibrotic pathologies where a pivotal role of TLR4-mediated inflammation has been observed.

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A new approach for direct visualization of unlabeled lipid nanoparticles for intracellular pathway analysis

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LIPID NANOPARTICLES, CELLULAR INTERNALIZATION, NANOPARTICLE-CELL INTERACTION, ELECTRON MICROSCOPY

Ionizable lipid nanoparticles (LNPs) are the most clinically advanced non-viral nano-delivery system for therapeutic nucleic acids[1]. The potency of LNPs is testified by the development of patisiran in 2018 and Pfizer/BioNTech and Moderna's mRNA vaccines during the Sars-CoV-2 pandemic[2] [3]. Despite these successes, several challenges remain in mRNA delivery, including what is known as "endosomal escape". Indeed, reaching the cytosol is mandatory for the therapeutic activity of RNA molecules.

In this project hybrid Lipid/Gold NPs will be synthetized and their cell interactions properties will be characterized through in vitro experiments, such as conventional and innovative light and electron microscopy techniques. Lastly, Ultrafast Electron Microscopy (UEM) will be used to gain further insights in the intracellular trafficking pathways of LNPs.

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A look at neurogenesis in Smith-Magenis syndrome: what goes wrong?

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SMS, HIPSCS, HINSCS.

Smith-Magenis syndrome (SMS)[1] is a rare, incurable and difficult to diagnose neurodevelopmental disorder characterised by physical, metabolic, behavioural, cognitive and sleep-wake cycle abnormalities. SMS is caused by haploinsufficiency of the RAI1 gene, due to either a deletion of the short arm of chromosome 17 (17p11.2) or a mutation within the RAI1 gene. The role of RAI1 and the molecular mechanisms underlying the disease are still largely unknown. Based on previous results obtained in SMS fibroblasts[2], we characterised and studied patient-specific human induced neural stem cells[3] (hINSCs) with the aim to highlight those aberrant processes that lead to the onset of phenotype.

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Exploring anti-aging and neuroprotective properties of plant extracts and their bioactive compounds in eukaryotic models of Parkinson's disease

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BIOACTIVE MOLECULES, PARKINSON'S DISEASE, NEURODEGENERATION, PROTEIN AGGREGATION, ANTI-AGING

Aging and age-related neurodegenerations are among the main challenges in modern medicine. Parkinson's disease (PD), associated with the misfolding of α-synuclein protein, affects about 10 million people worldwide[1]. In recent years, the protective effects of several plant-derived bioactive compounds have been highlighted on a wide variety of diseases, such as neurodegenerative diseases[2]. The valorization of the huge Italian flora biodiversity is one of the main goals of the National Biodiversity Future Centre (NBFC). To identify still unexplored bioactive molecules with potential neuroprotective and anti-aging properties, the extracts of 63 Italian endemic plants were screened on eukaryotic models of Parkinson's disease expressing human α-synuclein. The selected 4 plants and their components are now under investigation to elucidate the underlying mechanisms that contribute to the prevention and inhibition of α-synuclein aggregation.

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Targeting Hexosamine Biosynthetic Pathway to Overcome Resistance in Pancreatic Cancer Treatment

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PANCREATIC CANCER, HEXOSAMINE BIOSYNTHETIC PATHWAY, DNA DAMAGE

Pancreatic cancer (PC) is the seventh leading cause of cancer deaths, with nearly 80% diagnosed at advanced stages. Gemcitabine (GEM) is the primary treatment, but resistance necessitates alternative therapies. PC's metabolic changes upregulate the Hexosamine Biosynthetic Pathway (HBP), producing UDP-N-acetylglucosamine for protein glycosylation. FR054, a small-molecule inhibitor of PGM3 (an HBP enzyme), impairs cancer cell survival by activating the unfolded protein response, increasing ROS, and initiating apoptosis. Combining GEM with FR054 is well tolerated and nearly halts tumor growth in xenograft and patient-derived xenograft (PDX) models. FR054 enhances GEM's efficacy by promoting apoptosis through increased DNA damage and altered DDR protein phosphorylation. This study supports exploring HBP inhibitors to improve chemotherapeutic efficacy and overcome PC chemoresistance.

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Applying phylogenetic methods to identify plants with high drug discovery potential

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PHYLOGENETIC, MEDICINAL PLANTS, BIOSPROSPECTING

Some plants contain useful molecules for human health but identifying them requires time and resources. To optimize the discovery of new useful compounds, a strategic approach is needed to first select plants with high potential. A strategy is the phylogenetic one, as closely related plant species tend to share biochemistry. The aim is to propose a pipeline of phylogenetic methods to identify plants most likely to contain beneficial molecules. Five monophyletic subtrees were extracted from a phylogenetic tree containing 32.223 species from literature. 27 medicinal plants data correlated with a disease or biological activity were downloaded from two databases. All the data for all the subtrees were subject to a series of phylogenetic methods. The results identified the "hot nodes", nodes related to the plants with most potential, and the subtree descending from these nodes were plotted. This work was able to apply a phylogenetic strategy to select the plants with most potential.

Posters

p1. Health and Biodiversity

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Mapping the microbiome of hospitals and patients for solutions in risk monitoring

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HOSPITAL MICROBIOME, NOSOCOMIAL INFECTIONS, PATHOGENS

Hospitals are environments with a unique microbial composition due to the continuous exchange of bacteria between the urban environment and the people frequenting these places, combined with the high use of antimicrobial agents and an enhanced cleaning schedule. This creates a mix of species responsible for the nosocomial infections. As part of the ANTHEM project, we aim to characterize the hospital's microbiome and the spread of antimicrobial resistant bacteria in hospital settings. We collected samples and data from patients, and from different environmental sites of the pre-admission ward at different times of the day. Additionally, we collected samples from the intensive care unit and from other select wards at different times of the year. By integrating our results with a meta-analysis of hospital environmental microbiome, the long-term aim of the project is to help build fast and easy-to-use technological devices to monitor selected nosocomial pathogens.

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Wild bees adaptation to anthropogenic habitats: a multi-Omic approach to implement innovative conservation and ecological transition strategies

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POLLINATORS, URBANIZATION, METABOLOMIC, TRANSCRIPTOMIC, GENOMIC

Pollinators are essential in ensuring ecosystem functionality, yet the expansion of urban areas is affecting their biological and functional diversity, favoring those species able to adapt to anthropized habitats. In this framework, our aim is to understand the effect of urbanization on three wild bees widely distributed in Italian cities, through a multi-omic approach. Our workflow consists of obtaining and comparing genomic, transcriptomic, metabolomic, and metagenomic data originating from individuals collected in areas characterized by different degrees of urbanization. At the end of the sampling campaign we got 120 specimens for each species and processed a subgroup of samples. Metabolomic data are consistent with transcriptomic data, showing differences between samples collected in semi-natural and urban areas while revealing a shift towards metabolisms involved in adaptation patterns. Integrating these omic data will help in improving conservation strategies for pollinators.

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Tools of industrial ecology for the sustainability assessment of Nature-based Solutions

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URBAN GREENING, ENVIRONMENTAL BENEFITS, LIFE-CYCLE THINKING

In global development challenges, policies need to address sustainable development from an urban perspective. The EU aims to address this with Nature-based Solutions, providing benefits in the form of Ecosystem Services (ES)[1]. The integration of ES in industrial ecology tools like LCA can describe ES supply flows and ecosystems' ability to generate services, balancing the impacts caused by the interventions[2]. These principles have been applied to a case study of nature-based redevelopment in the Bicocca University campus. Here, trees, shrubs and herbaceous species have been planted in new enlarged green spaces to deliver multiple benefits. After the collection of data for the LCA, the results will be integrated with site-specific data (heat sensors, plant physiology analysis, irrigation and pollinators monitoring) to better understand the ES accounting in urban settings, the life-cycle performance of the greening project and its ability to answer to specific urban challenges.

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Enhancement of microbial biodiversity to promote environmental and human health

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MICROBIAL BIODIVERSITY, MICROBIAL BIODEGRADATION, SYNTHETIC POLYMERS, KOMBUCHA AND POSTBIOTIC

Microbial biodiversity is crucial for human and environmental health. My PhD project explore the role of microbial biodiversity with two objectives: (i) find new enzymes activities for synthetic polymer biodegradation, important for environmental health[1], and (i) assessing the postbiotic potential of microorganisms in fermented foods like kombucha, because, according to biome depletion theory[2], we have a reduced exposure to microbial factors. This reduced exposure destabilizes the immune system and gut microbiota, causing allergies, autoimmune diseases, and gastrointestinal disorders. To achieve my goals, I will conduct a functional metagenomic analysis of microorganisms from environmental samples, used for polymer degradation, and from kombucha. These analyses allow us to measure microbial biodiversity and potential functions. Subsequently, biodegradation tests will address the first objective, and in vitro analyses with human cell lines will address the second one.

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p5. Industrial Biotech

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Engineering microbial cell factories for biomanufacturing chemicals and modified natural polymers suited for the formulation of high performance elastomeric nano compounds

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TYRE, BACTERIAL CELLULOSE, SACCHAROMYCES CEREVISIAE ENGINEERING

Tyres are composed by many different materials, mostly derived from fossil sources[1] . Pirelli & C. S.p.A., leader of tyre technological innovation, aims to generate more environmentally sustainable products; one strategy is the substitution of the fillers.
The final goal of the project is to obtain modified cellulose useful in the formulation of high performance elastomeric nano-composites exploiting a biomanufacturing approach: natural microbial cellulose producers will be the chassis for further development on the material, while other cell factories will be used for producing enzymes and functionalizing agents.
During the first year, Komagataeibacter sucrofermentans was exploited as natural cellulose producer, and different production conditions have been tested to create an internal benchmark. In parallel, different engineered strains of Saccharomyces cerevisiae were tested for the production of lactic acid, a chemical platform that can be used to enhance the properties of cellulose

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Biotechnological approaches to support sustainable agriculture

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ENZYME PRODUCTION; AGROPHARMACEUTICALS; FERMENTATION; PEST CONTROL

Crop production challenges arise with the rise in global population. Plants commonly used in agriculture are susceptible to attacks by pests, causing significant annual food loss globally[1] . Chemical pesticides are a good way to control pests, however they have been proved to be harmful for the environment[2]. SIPCAM-OXON, an Italian company focusing on agriculture, innovative and sustainable crop protection products, and fine chemicals founded the PhD project, that will focus on three separate strands:
1) Design and synthesis of an enzyme in Komagataella phaffii, to produce a building block of a more complex molecule with agro pharmaceutical properties.
2) Optimization of growth mediums and conditions for production in liquid culture of fungal spores, used for pesticide control.
3) Production of agrochemicals, normally extracted from plant material, via plant cell fermentation or engineering of microbial strains.

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Development of Organ-on-Chip Based Methodologies for in Vitro Novel Compound Testing

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ORGAN-ON-CHIP, MIVO, NOROVIRUS, INTESTINAL MODEL, DYNAMIC FLOW

Norovirus, a highly contagious cause of severe gastroenteritis, lacks effective treatments. This PhD project, part of GlycoNoVi, focuses on understanding norovirus replication and developing new models. Despite its impact, much remains unknown about the virus, including its entry mechanism and how it replicates. Additionally, animal reservoirs like pigs and dogs raise concerns about cross-species transmission. These knowledge gaps hinder treatment and vaccine development. Traditional 3D cell cultures, while showing progress, lack a crucial factor: dynamic flow, which mimics the human intestine's natural environment. To address this, we will use the MIVO® organ-on-chip platform with patient-derived intestinal tissues to model virus-cell interactions and unlock new avenues in norovirus research.

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Investigating the role of the SOWAHC-DIAPH1 complex in physiology and cancer

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CELL MOTILTY, ACTIN CYTOSKELETON, PROTEIN-PROTEIN INTERACTION

Lamellipodia and ruffles are actin-based cell protrusions involved in the mesenchymal mode of migration of normal and diseased cells. The group has previously demonstrated that mammalian Diaphanous formin (mDia1) is required for the formation of these protrusions (1). This doctoral project primarily investigates the regulation of mDia1 focusing on the poorly characterized protein SOWAHC (Sosondowah Ankyrin Repeat Domain Family Member C), which we have shown to be a novel interactor of the former. Studying the machinery that leads to the formation of lamellipodia and ruffles can increase our understanding of human diseases and other physiological processes relying on cell motility.

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Preliminary data of ICV delivery of human Neural Stem Cells in a mouse model of ALS

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NEURAL STEM CELLS, ALS, SOD1, METABOLISM

Amyotrophic lateral sclerosis (ALS) is a relentlessly fatal neurodegenerative disease leading to a rapid paralysis and death[1]. To date, the precise primum movens and an effective therapy are still lacking. Concerning this, we are investigating the use of intracerebroventricular (ICV) transplantation of hNSCs as a less-invasive method for cell delivery in the nervous system using athymic and SOD1G93A mice. Our initial data show that the ICV transplant is well tolerated. The behavioral and histopathological analysis performed on cervical and lumbar parts of the spinal cord suggest a slight positive trend in the hNSCs transplanted group compared with the controls. In parallel, we are elucidating the metabolic profile of ALS cells derived from human induced Neural Stem Cells (hiNSCs) aiming to provide a platform to unravel the pathological mechanisms underpinning ALS and to test insightful therapeutic strategies. Nevertheless, further studies are necessary to confirm these hypotheses.

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Exploring the function of the CST complex at DNA double-strand breaks

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YEAST, GENOME STABILITY, DNA DAMAGE, CHECKPOINT, CST COMPLEX

DNA double-strand breaks (DSBs) are cytotoxic lesions that must be repaired to preserve genomic integrity. Following DSBs, cells activate a signal transduction pathway, known as DNA damage checkpoint, whose apical checkpoint kinases are Tel1 (ATM in humans) and Mec1 (ATR in humans). In Saccharomyces cerevisiae, these checkpoint kinases, once activated, promote DNA damage repair and support DNA replication under stress conditions[1]. The Cdc13-Stn1-Ten1 (CST) complex is known to be involved in telomere maintenance[2]. Interestingly, we found that the lack of Stn1 C terminus exacerbates the DNA damage sensitivity of mec1 and tel1 mutant cells, whereas a stn1 missense mutation suppresses it, suggesting a role for this protein in supporting the functions of these checkpoint kinases in DNA damage repair. We will investigate the molecular mechanisms of these genetic interactions to understand the role of Stn1 in checkpoint activation.

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Interaction between myofilament and SERCA2a activators on heart muscle mechanics

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DRUG TARGETS IN HEART FAILURE; CA2+ HANDLING; SERCA2A ACTIVATORS; MYOFILAMENT ACTIVATORS.

Direct stimulation of myofilament function is a promising strategy for treating heart failure, but it may impair diastolic function by slowing sarcomere relaxation. Activating SERCA could mitigate this issue while enhancing inotropic effects. To test this hypothesis, we aim to study the interaction between a SERCA (Istaroxime, ISTA) and a myofilament (Levosimendan, LEVO) activator on excitation-contraction coupling in mouse cardiomyocytes. First, we assessed the individual effects of these drugs on Ca 2+ dynamics. As expected, ISTA stimulates SERCA2a activity. Interestingly, LEVO acts similarly, likely mitigating the SERCA-PLN interaction in a PKA-dependent manner.By combining the two, this effect is preserved, although it does not appear to reflect an additive impact. These results suggest the potential for complementary use of ISTA and LEVO. Future studies will investigate whether their combination can effectively enhance both inotropy and lusitropy in an energetically efficient way.

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Multi-omics data analysis to characterize sex-specific metabolic shifts during embryo development

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DYNAMIC METABOLIC MAPS, STEADY-STATE MODELS, EMBRYONIC STEM CELLS

Recent findings suggest that cell metabolism may be key to understanding miscarriages and developmental abnormalities in early embryonic development[1–6]. To explore metabolic differences between pre- and post-implantation embryonic cells, we analyzed single-cell RNA-seq data from different 3D culture models. We integrated data coming from two studies, one using Inner Cell Mass Cells[7], the other using human Embryonic or induced Stem Cells[8]. We leveraged metabolic network reconstructions, constraint-based methods[9], and machine learning techniques[10] to estimate the fluxes. Preliminary results revealed notable variations in metabolic activity, particularly in biomass production and glucose consumption. However, the metabolic differences across experiments were not always consistent, indicating the need for further investigation and a refinement of the computational approach to better understand embryonic metabolism and its implications for early developmental processes.

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Synthesis, Conformational Analysis and Preliminary Biological Evaluation of Iminosugar-based Pharmacological Chaperones for Mucopolysaccharidosis Type I

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IMINOSUGARS, CHAPERONES, MPS I, IDUA, LSDS

In recent years L-iduronic acid-type piperidines have emerged as promising active-site pharmacological chaperones of the lysosomal glycosidase α-L-iduronidase (IDUA). IDUA deficiency is involved in a neurodegenerative lysosomal disorder known as Mucopolysaccharidosis type I. In this context, we present a novel synthetic approach for the preparation of a series of analogues of L-iduronic acid. Furthermore, a complete computational conformational analysis supported the NMR-based evidence that the introduction of an acyl- or alkyl- moiety at the nitrogen position can be exploited to modulate the conformation of these small molecules. Finally, a preliminary biological evaluation of their chaperoning ability on COS-7 cells exhibited a significant increase in IDUA activity in comparison to the untreated control. This behaviour indicate that these molecules can cross the plasma membrane, the endoplasmic reticulum membrane, and recognize and bind the specific target which were designed for.

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Identification and characterization of anti-amyloidogenic natural compounds for the prevention of age-related neurodegenerative diseases

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AMYLOID-B, ANTI-AMYLOIDOGENIC COMPOUNDS, NATURAL EXTRACTS, FLAVONOIDS

Several neurodegenerative disorders, such as Alzheimer's disease, are characterized by the accumulation of extracellular insoluble fibrillar aggregates that lead to synaptic dysfunction and nerve cell death. Compounds capable of binding and preventing Aβ peptide aggregation, such as flavonoids or epigallocatechin gallate, occur ubiquitously in plants and vegetables and exert neuroprotective effects[1–4].

Since plant-derived extracts are rich in phenolic compounds[5], we have characterized by NMR and LC-HRMS various aqueous, alcoholic and hydro-alcoholic extracts of Myrtle leaves, searching for potential anti-amylodogenic compounds, as putative molecular tools for the prevention of neurodegenerative disorders[6 7].

To better elucidate these mechanisms, large quantities of purified Aβ peptide are required. Here, we also present a first attempt to express and purify recombinant Aβ1-42 in E. coli, which could lead to satisfactory yield and purity.

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Invited Speakers

is1.

Prof. Francesco Iorio
Human Technopole

CRISPR-based second-generation of genetic-vulnerability-maps in cancer cells

Francesco Iorio[1]
[1] Human Technopole

I will focus on the use of genome-wide CRISPR-Cas9 viability reduction screens performed on large panels of cancer in-vitro models as a means to identify and characterise cancer genetic dependencies, alongside their exploitation through dedicated bioinformatic prioritisation pipelines for the discovery of new therapeutic targets and markers.
Beginning with a seminal work that led to the identification of WRN as a target for colorectal cancers with microsatellite instability, I will detail our subsequent efforts in demonstrating the reproducibility and computational integrability of large inter-study CRISPR-derived cancer dependency datasets. Additionally, I will showcase a variety of computational tools developed by my team, instrumental in facilitating CRISPR data analysis and interpretation.
My narrative will culminate in the unveiling of a novel generation of cancer dependency maps and target prioritisation pipelines, built upon integrated inter-study CRISPR-based cancer dependency datasets and incorporating advanced computational analysis of transcriptomic data and network models. Finally, I will provide a brief overview of our recent ERC-funded DepSHOCK and AIRC-funded Drug Sensitivity Recovery map projects, which will enrich current Cancer Dependency Map efforts with new data modalities and computational paradigms

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Beyond the black-box: A practical guide to technical interpretability

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Artificial Intelligence, and Machine Learning (ML) in particular, is a very popular approach to turn (labeled) datasets into predictive models. Although effective, the inner workings of ML models are generally unknown, especially in the case of very complex neural networks. In other words, they are black-boxes, which can be dangerous when used to drive decisions in high-risk applications because the rationale of predictions is completely unknown, and users have the right to an explanation. Is the lack of an explanation a real problem? What is an explanation, exactly? Shall we drop ML altogether, or can we use it under some circumstances? Alas, none of these fundamental questions will be really answered during this talk, although the audience will be continuously challenged to give a solution to this puzzle. On the contrary, I will propose a different approach, based on the idea of building models that are intrinsically interpretable by the user. In particular, I will present the latest advancements of pyFUME, our python tool for the development of compact and interpretable AI systems, built by integrating ML, fuzzy logic, evolutionary computation, and swarm intelligence. I will conclude the talk by showing some concrete (and real-time) examples.

The AI Act and the right to technical interpretability

Chiara Gallese[1]

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What is interpretability from the legal and ethical point of view? How do the legal provisions in the EU regulate black boxes? The talk will highlight the role of the most recent EU regulation on AI systems, the AI Act, which introduces a new right to explanation for automated decision-making, complementing GDPR, the EU regulation regulating personal data, and Convention 108+, the only binding international instrument regarding data protection. The author will consider the philosophical theories related to the scientific explanation and the role of the causal link in the debate around AI opacity.

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