

Selected Lectures of the Conference “New Approaches and Technologies – From Fetus to Adult”

CAGLIARI (ITALY) • OCTOBER 25TH, 2025

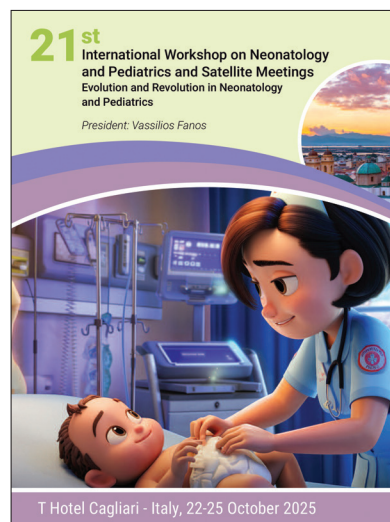
The Conference “New Approaches and Technologies – From Fetus to Adult” is a Satellite Meeting of the 21st International Workshop on Neonatology and Pediatrics, Cagliari (Italy), October 22nd-25th, 2025.

PRESIDENTS

Vassilios Fanos (Cagliari, Italy), Osama Al Jamal (Cagliari, Italy), Viviana Marinelli (Cagliari, Italy), Gianfranco Trapani (Sanremo, Italy)

FACULTY

Osama Al Jamal (Cagliari, Italy), Simona Alessandri (Rome, Italy), Antonio Colangelo (Trento, Italy), Vassilios Fanos (Cagliari, Italy), Grazia Fenu Pintori (Sassari, Italy), Donatella Gariel (Cagliari, Italy), Karolina Krystyna Kopeć (Krakow, Poland, and Cagliari, Italy), Danila Manus (Cagliari, Italy), Viviana Marinelli (Cagliari, Italy), Carla Marzetti (Bologna, Italy), Francesca Mondello (Rome, Italy), Giovanni Monni (Cagliari, Italy), Antonio Noto (Cagliari, Italy), Paola Palanza (Parma, Italy), Silvia Petza (Cagliari, Italy), Roberta Pintus (Cagliari, Italy), Maria Luisa Ricci (Rome, Italy), Giorgio Terziani (La Spezia, Italy), Gianfranco Trapani (Sanremo, Italy), Marco Valentini (Faenza, Italy)



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How to cite

[Lecture's authors]. [Lecture's title]. In: Selected Lectures of the Conference "New Approaches and Technologies – From Fetus to Adult"; Cagliari (Italy); October 25, 2025. *J Pediatr Neonat Individual Med*. 2025;14(2):e140219. doi: 10.7363/140219.

LECT 1

NEW ASSISTED REPRODUCTIVE TECHNOLOGY (ART) TECHNIQUES TO INCREASE THE BIRTH RATE IN SARDINIA: MEDICAL-SOCIAL FREEZING AND HETEROLOGOUS FERTILIZATION

G. Monni

ART Center – Genera, Cagliari, Italy

Population decline in the Western world is steadily and progressively increasing, with very low birth rates (1.20), and is expected to decline by approximately one-third by 2100. In Italy, the birth rate in 2024 reached an all-time low (1.18 children per woman), and the age at first birth is increasingly advanced (33 years, in Sardinia 34 years).

In recent years, despite immigration and government economic and social policies, the fertility rate has not improved, as women increasingly seek children at older ages. In fact, oocytes after the age of 40 increasingly present with chromosomal disorders, resulting in a progressive decline in fertility and an increase in embryonic pathologies.

New assisted reproductive technology (ART) procedures (Medical-Social Freezing and Oocyte and Sperm Donation) can be an advantage and a method for attempting to reduce infertility.

In Medical-Social Freezing, oocytes are collected at a young age and cryopreserved, allowing women to delay pregnancy and choose the most favorable time, thus utilizing young cryopreserved oocytes and planning a pregnancy up to age 50.

Another technique that allows pregnancy to be achieved even in women with poor ovarian reserve or in menopause, or after age 43, is Heterologous Fertilization via Egg Donation. This technique offers an increasing number of women the opportunity to achieve a pregnancy that would otherwise be impossible.

These last two techniques, along with Preimplantation Genetic Diagnosis, which enables doctors to transfer only healthy embryos unaffected by age-related chromosomal disorders, play a crucial role in increasing birth rates.

From June 2024 to July 2025, at the Genera Center in Cagliari, in addition to all traditional ART techniques, these new procedures described above were introduced, which have further contributed to the birth rate in Sardinia.

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LECT 2

RENAL REGENERATIVE MEDICINE: WHAT DID WE LEARN?

G. Faa¹, V. Fanos^{2,3}

¹*Professor Emeritus, Department of Medical Sciences and Public Health, University of Cagliari, AOU Cagliari, Cagliari, Italy*

²*Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy*

³*Department of Surgical Sciences, University of Cagliari, Cagliari, Italy*

The incidence of prematurity is increasing around the world, being associated with short-term and long-term complications. Regarding the long-term consequences, according to Barker's hypothesis, the interruption of physiological tissue and organ development might influence susceptibility to developing multiple diseases later in life, including kidney diseases.

Our nephron burden is conditioned by the intra-uterine environment, including maternal malnutrition and maternal drug exposure, and by the weeks of gestation and body weight at birth. Extreme immaturity at birth is associated with impaired nephrogenesis and oligonephronia, which will be maintained in childhood and in adulthood.

A low nephron number is considered one of the most relevant factors in shaping our susceptibility to severe kidney diseases and kidney failure in adulthood. A kidney with a high number of glomeruli (2 million) can withstand the injuries that may occur during its lifespan. In contrast, a kidney with 10-fold fewer

glomeruli will be less able to counteract additional injuries, ultimately leading to renal insufficiency. Fifteen years ago, our group pioneered a new approach: initiating regenerative medicine in preterm and low-birth-weight infants during the perinatal period, specifically within the 2 weeks after birth. Our proposal began from an “embryological” view of adult kidney diseases, in which susceptibility to developing chronic kidney disease starts *in utero*, being primarily related to an abnormal programming of kidney development. Our “physiological regenerative” approach focused on the induction of pluripotent stem/progenitor renal cells to generate new nephrons during the perinatal period. Preliminary data in experimental animals have shown that thymosin beta 4 (TB4), an endogenous peptide with regenerative effects, administered to pregnant mothers, acts as a powerful fetal growth promoter, accelerating the development of newborn organs, including the kidneys. TB4 might act by stimulating the abundant stem/progenitor cells present in the fetal kidneys, which represent an optimal target for starting a regenerative medicine in the perinatal period. Since TB4 is a natural compound, this regenerative approach could be defined as “physiological regenerative medicine”.

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LECT 3

TRANSLATIONAL POTENTIAL OF ESSENTIAL OILS AND NANOCARRIERS IN ANTIMICROBIAL THERAPY: NOVEL STRATEGIES FROM FETAL TO ADULT LIFE

F. Mondello¹, M. Di Vito², M.L. Ricci³

¹President of the Italian Society for Research on Essential Oils (SIROE), Rome, Italy

²Department of Basic, Clinical, Intensive Care and Perioperative Biotechnology Sciences, Università Cattolica del Sacro Cuore, Rome, Italy

³National Reference Laboratory for Legionella, Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy

The global rise of antimicrobial resistance poses a significant threat to effective infection control across all age groups, from neonates to adults [1]. While the pharmaceutical industry has traditionally deprioritized the development of new antibiotics, the growing limitations of current drugs have stimulated interest in integrative or alternative approaches, particularly those based on natural compounds. Essential oils (EOs), complex mixtures of volatile bioactive components extracted from aromatic plants, have shown promising *in vitro* antimicrobial, anti-inflammatory, and antivirulence effects [2]. Their activity includes inhibiting bacterial growth, interfering with quorum sensing, and disrupting the formation of biofilms. However, their volatility, low water solubility, and chemical instability hinder direct clinical application. Nanotechnological advances have enabled the development of EO-loaded nanocarriers that improve pharmacological profiles by increasing stability, solubility, and targeted delivery. These nanoformulations have demonstrated enhanced efficacy against multidrug-resistant pathogens, such as *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli*, in preclinical models [3]. Moreover, encapsulation may reduce toxicity and degradation, improving tolerability even in vulnerable populations. Despite these encouraging findings, most available data remain preclinical, and little is known about potential synergistic or antagonistic interactions between EO components or with standard antibiotics.

Furthermore, pediatric and neonatal applications are largely unexplored in formal trials, although EO-based products are widely used as over-the-counter remedies in mild infectious conditions. To support the transition of EOs from bench to bedside, robust translational studies are urgently needed. These should include mechanistic investigations, safety profiling, pharmacokinetics, and controlled clinical trials. With proper validation, EO-based nanoformulations could represent a new tool in the antimicrobial arsenal across the lifespan – from fetal protection to adult care.

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LECT 4

THE EUROPEAN LIFE MILCH PROJECT: WHERE DO WE STAND?

P. Palanza¹, V. Fanos², A.M. Papini³, S. Perrone^{1,4}, T. Ghi^{1,4}, S. Paterlini¹, M.M. Brambilla^{1,4}, D. Baccolo¹, C. Scopa¹, A. Ardenghi¹, A.M. Shulhai^{1,4}, C. Caffarelli^{1,4}, F. Nuti³, F. Fernandez³, C. Sartori⁵, F. Alberghi⁵, B. Righi⁵, M. Fontana⁴, L. Filonzi⁶, C. Petrolini⁴, B. Piccolo⁴, E. Turco⁴, R. Pintus², C. Piras², S. Petza², A. Dessi², F. Nonnis Marzano⁶, D. Ponzi¹, A. Pelosi¹, M.E. Street^{1,4,5}

¹Department of Medicine and Surgery, University of Parma, Parma, Italy

²Department of Surgical Sciences, University of Cagliari, Cagliari, Italy

³Department of Chemistry "Ugo Schiff", University of Florence, Florence, Italy

⁴Azienda Ospedaliero-Universitaria, Parma, Italy

⁵Azienda AUSL-IRCCS, Reggio Emilia, Italy

⁶Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy

Many chemicals present in the environment can act as endocrine disruptors (EDs) and alter the normal function of the endocrine system even at very low doses during critical developmental periods. Currently, EDs represent one of the most epidemiologically relevant factors associated with an increased risk for metabolic, reproductive and neurobehavioral disorders [1, 2]. EDs are ubiquitous, and maternal exposure to EDs during pregnancy and lactation results in fetal exposure through the placenta and neonatal exposure through breastmilk, which is the best source of nutrition for infants. Still, it can be contaminated by these lipophilic chemicals [3]. The Life MILCH project (Mother and Infant dyads: Lowering the impact of endocrine disrupting Chemicals in milk for a Healthy Life – www.lifemilch.eu), is a longitudinal study aimed at reducing the impact of EDs on human health by assessing exposure and effects on mother-child pairs, with breastmilk as a primary biomarker of environmental exposure. In the first biomonitoring phase of the project, 690 pregnant women were recruited from three Italian locations (Parma, Reggio Emilia, and Cagliari) and followed up with their children at 1, 3, 6, and 12 months of age to assess infant development and collect urine

and breast milk samples. At any given time point, mothers completed questionnaires on their lifestyle and nutritional habits. Biological samples were analyzed for 13 different EDs and their metabolites. Significant negative associations were found between maternal bisphenol levels and infant socio-emotional behavior at 3 months, and between maternal phthalate and bisphenol levels and neurodevelopmental scores at 6 and 12 months of age. Levels of EDs in maternal urine and breastmilk, and in infant urine, were significantly associated with mothers' lifestyle and diet to identify possible primary sources of maternal exposure to EDs and establish a risk assessment model.

Based on this evidence-driven model, the project has developed a targeted prevention/awareness campaign, as well as interventions to reduce maternal exposure to EDs. The efficacy of the prevention campaign was assessed by monitoring the levels of EDs in the breast milk of a new group of enrolled women (n = 160) who had previously participated in the campaign during pregnancy/nursing. When the analysis of these biological samples is completed, we will compare the results obtained in the 2nd screening with those obtained in the 1st screening to understand the impact of specific interventions on the levels of individual exposure to environmental EDs. The project hypothesis is, indeed, that targeted changes in nutritional habits and lifestyle could reduce the levels of specific EDs in the mothers, their breastmilk and, consequently, in the infants, thus soliciting more effective regulatory actions to reduce the presence of EDs in the environment and protect the vulnerable population of mothers and children.

ACKNOWLEDGEMENTS

LIFE18 ENV/IT/000460. Life MILCH: Mother and Infant dyads: Lowering the impact of endocrine disrupting Chemicals in milk for a Healthy Life.

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Rheumatology Service – Osteoporosis Center, S. Pier Damiano Hospital, Faenza (RA), Italy

LECT 5

METABOLOMICS AND NUTRITION

S. Alessandri

Nutritionist Biologist, Rome, Italy

Precision Nutrition is currently one of the most promising challenges in translational medicine, as it requires tools capable of capturing the body's functional state in real-time and transforming it into personalized dietary strategies. Among the “omic” sciences, metabolomics has established itself as a key technology, providing a dynamic map of the biochemical processes that link nutrients, metabolism, and health.

In recent years, metabolomic profiles have demonstrated the ability to identify mitochondrial dysfunctions, micronutrient deficiencies, and alterations in detoxification systems, enabling targeted and measurable interventions. The analysis of organic acids enables the identification of functional blocks in the Krebs cycle and β -oxidation, guiding the rational use of vitamin cofactors and nutraceutical supports. Functional biomarkers, such as methylmalonate, glutarate, and pyroglutamate, among others, also offer an objective approach to assessing vitamin and glutathione status.

An additional added value is the metabolomic reading of the microbiota: through metabolites derived from microbial activity (e.g., SCFA/BCFA, indoles, p-cresol, phenols), it is possible to infer patterns of fermentation/putrefaction, oxidative stress, and conjugation pathway loads, integrating the information with the clinical picture and guiding nutritional and nutraceutical modulation.

From this perspective, metabolomics is not only a diagnostic tool but also an operational bridge between biochemistry and clinical practice, making Precision Nutrition a concrete and evidence-based practice.

LECT 6

METABOLOMICS IN RHEUMATIC DISEASES

M. Valentini

Despite significant advances in the diagnosis and treatment of rheumatic diseases, there remain areas that are difficult to classify. First and foremost among these is fibromyalgia. Numerous clinical facets, along with the absence of a pathognomonic diagnosis, characterize this pathology. The complexity of this syndrome and the numerous overlapping conditions necessitate conducting investigations that can detect which systems are primarily involved and the profound alterations and interactions at the cellular/metabolic levels. A cross-talk between central and peripheral neuroinflammation, modulated by pathogens and intestinal opportunists, is widely described in the literature. The production of micromolecules by these pathogens causes pathological modulation of the glia, leading to neuroinflammation, which is a predominant feature in such clinical presentations. Psoriatic arthritis is the prototype of immunometabolic pathology. It is well known that, in addition to the cytokine alterations underlying autoimmune pathogenesis, this pathology presents a metabolic diathesis that masks the lack of response of these patients to standard protocols with disease-modifying antirheumatic drugs (DMARDs) and biologics. Furthermore, unlike rheumatoid arthritis, psoriatic arthritis presents five clinical variants and a heterogeneity of phenotypes that make it challenging to perform true precision medicine, which is now indispensable for the purposes of containing healthcare costs. Actual metabolic signatures of psoriasis and psoriatic arthritis are emerging in the literature. It is therefore likely that, in the near future, the metabolic networks in the subtypes of these patients will be identified and understood.

Connective tissue diseases manifest themselves with a variety of symptoms, the pathogenesis of which is complex to classify. Consider systemic lupus, which presents symptoms such as asthenia (with an immunometabolic imprint) or skin manifestations that also express infectious overlaps (fungi, bacteria). Immunometabolic alterations characteristic of systemic lupus erythematosus have been reported in the literature, ranging from difficulties in oxygen utilization during the Krebs cycle to mitochondrial distress and apoptosis deficiency. This cellular alteration is determined by non-canonical metabolic pathways, which explain the clinical complexity of this disease.

Primary osteoarthritis with calcinosis, representing an expression of a metabolic disease with immune manifestations *in situ*, also lacks laboratory diagnostics.

Finally, osteoporosis. This condition represents the first manifestation of a profound systemic alteration with serious implications for the individual's future health. The new challenge of modern rheumatology lies in precision diagnosis and therapy, the implementation of which requires equally precise diagnostics.

Metabolomics, through the study of specific chemical fingerprints left by cellular processes, i.e., the study of metabolic profiles, enables the detection of tiny molecules that cannot be identified with standard laboratory methods. The metabolome represents the set of all metabolites of a biological organism, which are the end products of its gene expression. And so, while mRNA gene expression data and proteomic analyses do not fully explain what might be happening in a cell, the metabolic profile can provide a snapshot of that cell's physiology. Furthermore, it provides clinicians with an overview of the condition and balance of systems, offering a snapshot of health/disease status. In conclusion, metabolomics currently represents the ideal laboratory method not only for understanding the pathogenesis of many rheumatic diseases, but above all, for providing clinicians with the “systemic view” that is essential for restoring rheumatic patients to a new state of health.

LECT 7

NEW APPROACHES IN AUTISM MANAGEMENT

M. Greco

High Training School in Epigenetics, Adaptive Neuropsychophysiology and Neuro-developmental Issues, Turin, Italy

Neurodevelopmental disorders, particularly autism spectrum disorder, are increasing at an exponential rate and represent a genuine social and healthcare emergency. This presentation explores new clinical and integrative approaches that emphasize the role of neuroinflammation – often underlying behaviors labeled as “problem behaviors” – and the need for medical assessments that consider their organic origins.

The gut-brain axis is examined, with a focus on intestinal permeability and blood-brain barrier dysfunction, which are exacerbated by dysbiosis,

persistent constipation, and inadequate eating habits. Key environmental and biological triggers are discussed, including pro-inflammatory foods, viral, bacterial, fungal, and parasitic infections, exposure to environmental toxins, toxic chemicals and hydrocarbons, heavy metals, and molds.

The presentation offers clinical tools for recognizing chronic parasitic states, epigenetically impactful nutritional strategies, detoxification techniques, and protocols for integrative support. Special attention is given to the first 1,000 days of life, a critical window for neuroimmune and metabolic programming.

LECT 8

METABOLIC DETERMINANTS IN FIBROMYALGIA SYNDROME STUDIED WITH THE EPIGENETIC METHOD

B. Pische^{1,2}, A. Scognamiglio², G. Terziani³, G. Fenu Pintori²

¹*Project e.INS – Ecosystem Of Innovation For Next Generation Sardinia, PhD School, University of Sassari, Sassari, Italy*

²*Department of Biomedical Sciences, University of Sassari, Sassari, Italy*

³*Disciplines of Wellness, Saint George School, Brescia, Italy*

Epigenetics is a multidisciplinary science that studies elements, both natural and artificial, capable of interacting with DNA. This study aims to highlight the role of epigenetics as a tool for identifying and monitoring factors that influence the progression of fibromyalgia syndrome. Using a device called SDRIVE, which employs an artificial intelligence system capable of processing signals emitted by cells in the hair bulb, epigenetics becomes central in research focused on the study of the syndrome, which has shown a marked increase in recent years. Through individual monitoring of epigenetic markers, the device provides highly informative data, highlighting the role of specific vitamins, minerals, fatty acids, antioxidants, and amino acids. The study followed a 90-day protocol, during which patients took Cellfood™, a supplement capable of modulating intracellular oxygen demand. The results indicate changes in the levels of the aforementioned factors, suggesting that the individual's metabolism, following supplementation, may be directed towards extracellular matrix clearance. This process involves, each for its own function: vitamins C and E, synergistic antioxidants that protect the cytosol, membranes, and extracellular

fluids from reactive oxygen species (ROS) while supporting collagen synthesis, neurotransmitter production, and lipid metabolism; minerals such as boron, calcium, and iodine, involved respectively in the regulation of bone and inflammatory metabolism, signal transduction, muscle contraction and coagulation, and gene and metabolic regulation through thyroid hormones; gamma- and alpha-linolenic acids-6 and oleic acid-9, which modulate membrane fluidity, pro- and anti-inflammatory eicosanoids, and energy metabolism; and amino acids such as proline, asparagine, and arginine, which contribute to collagen stabilization, the transfer and redistribution of the $-NH_2$ group between molecules (essential for biosynthesis, nitrogen metabolism, and detoxification), nitric oxide synthesis, and energy metabolism. The most likely hypothesis is that Cellfood™ induces overall metabolism to activate extracellular matrix clearance mediated by the elements whose bioavailability has been restored by the supplement.

ACKNOWLEDGMENTS

Project e.INS – Ecosystem Of Innovation For Next Generation Sardinia, missione 4 componente 2, “dalla ricerca all’impresa” investimento 1.5, creazione e rafforzamento di “ecosistemi dell’innovazione” costruzione di “leader territoriali di R&S” del piano nazionale di ripresa e resilienza (PNRR) finanziato dall’Unione Europea “Next Generation EU”.

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LECT 9

METABOLOMICS AND MICROBIOMICS IN CLINICAL PRACTICE

C. Marzetti

Valsambro Clinical Laboratory, Bologna, Italy

The growing spread of “omic” methods is transforming the approach to personalized medicine. In particular, metabolomics, through the analysis of metabolites downstream of cellular biochemical processes, provides a dynamic functional picture

of the patient’s state of health, highlighting alterations in energy cycles, nutrient metabolism, detoxification, and oxidative processes. At the same time, microbiomics allows us to characterize the composition and functionality of the gut microbiota, identifying dysbiosis, the presence of opportunistic pathogens, and relationships between microbial populations and host metabolism. The integration of metabolomics and microbiomics into clinical practice is a powerful tool for early diagnosis, prevention, and the personalization of therapeutic and nutritional interventions. This multidimensional approach enables molecular data to be linked to the clinical context, providing a systemic view of the interactions between the host and microbiota and opening up new perspectives in the management of chronic and complex diseases.

LECT 10

THE EPIGENETIC REVOLUTION IN THE AGE OF POLLUTION: INDIVIDUAL RESPONSIBILITY TOWARDS FUTURE GENERATIONS

G. Terziani

Disciplines of Wellness, Saint George School, Brescia, Italy

Epigenetics: why should we care? Because the way we think, feel, and care for ourselves, as well as the environment around us, influences our cells. Conversely, genetic alterations also influence the way we feel, think, and interact with others. An integrated clinical approach tailored to personalized, preventive, and above all, participatory medicine, is needed.

With the discovery of DNA, we believed that everything was written in our genetics and that nothing could be changed. Over the years, a new branch of genetics has emerged, known as “epigenetics”, which has allowed us to change our perspective completely. Epigenetics studies the interaction between our DNA and the environment, demonstrating how external factors change our gene expression, i.e., the way in which our genetic potential is expressed.

It is commonly assumed that the DNA in our cells fully determines our identity; however, the sequence of our genes does not encompass the entirety of our phenotypic expression. Epigenetics, the discipline that investigates regulatory mechanisms of DNA, demonstrates that the genetic structure is both dynamic and adaptable. Factors such as nutrition,

dietary supplementation, physical exercise, and psychosocial management represent modifiable variables through which epigenetic responses can be optimized, ultimately enhancing human well-being. The most interesting aspect of epigenetic modification is that it can occur in response to external environmental stimuli that influence the environment around us and our lifestyle. In a sense, epigenetic modification is an adaptive change that cells make. DNA is not a destiny. It is a personal responsibility to be aware of the factors that can damage or protect our health.

Today, we have numerous technologies, such as metabolomics, that can guide professionals in their work. One of the latest developments on the world stage is the mapping of epigenetic factors, and one of the most interesting biomarkers is undoubtedly the hair bulb and the hair itself. In this regard, the analysis of hair samples is considered by the World Health Organization to be one of the most important biological matrices for estimating the degree of human exposure to certain toxic elements. It should also be noted that, compared to blood, nails, urine, and saliva, hair has the advantage of greater stability, ease of collection, transport, and storage, as well as representing a “biological dosimeter” of long-term individual exposure (months and even years in some cases) and high concentrations of metals.

SDRIVE technology has been studied in various populations, including centenarians, athletes, and individuals with fibromyalgia. It is proving to be an added value in an integrated clinical approach aimed at 4P medicine and, above all, at the role of personalized and individualized medicine. In addition, based on the results of the analysis, the test also offers a 90-day treatment protocol that structures our diet, specific nutritional deficiencies, which foods to avoid or include, which environmental interferences are harming us (e.g., additives, toxins, metals, radiation), and how to resolve them by modifying our environment and taking specific supplements. All of these solutions can significantly transform our level of well-being. Harmful signals from the environment negatively modify the phenotype without altering the genotype. This change is reflected in our physiology. These signals include toxins received from our parents during pregnancy, medications, food, the air we breathe, electromagnetic radiation, and even the thoughts and emotions we have daily. We need to make pregnancy safe by reducing harmful

interference, such as pesticides in the food chain, air pollutants, and maternal-fetal stress. Medicine should increasingly shift toward primary prevention rather than therapy.

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LECT 11

ARTIFICIAL INTELLIGENCE: FRIEND OR FOE?

A. Colangelo

GPI, Trento, Italy

Imagine a living organism that appeared on Earth millions of years ago. A simple organism, consisting of a single cell. Its natural objectives (we might call them unconscious – or perhaps consciousness coincides with the necessity of living?) are undoubtedly to survive and to reproduce (a form of natural programming: DNA). Yet, its environment inevitably imposes challenges: it must compete with its peers for external resources. For instance, if light filters through a gap between the leaves, our organism and all its counterparts will tend to move toward the light, as they require it for photosynthesis, thereby competing for vital space. At this point, some organisms will succeed in positioning themselves, perhaps entirely by chance, in what we might call a “place in the sun”, in an optimal location, while others will not, as part of the competition for life. What, then, has enabled the better-positioned organism to enjoy such an advantage? Possibly any random characteristic that distinguished it. In essence, this illustrates the concept of species evolution.

The central question of this reflection is whether an analogy can be drawn between a large language model (LLM) and a basic organism. Can we expect to observe phenomena of adaptation? In other words, what we are proposing is a vision that may appear paradoxical, yet is far from unrealistic, one that suggests genuine analogies, at a behavioral level, between the state of nature and the evolution of living species, and the dynamics of an LLM artificial intelligence.