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Lectures

Selected Lectures of the Meeting "From the First Thousand Days to Aging: Life is a Continuum. Epigenetics, Artificial Intelligence and Environmental Impact"

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The Meeting "From the First Thousand Days to Aging: Life is a Continuum. Epigenetics, Artificial Intelligence and Environmental Impact" is a Satellite Meeting of the 20th International Workshop on Neonatology and Pediatrics, Cagliari (Italy), October 23rd-26th, 2024.

FACULTY (GERMANY AND ITALY)

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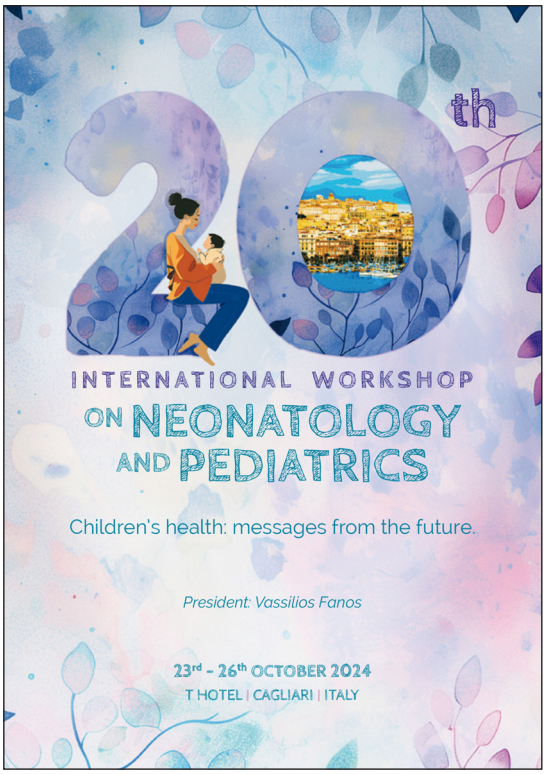

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LECT 1

THE POWER OF EPIGENETICS IN THE FIRST THOUSAND DAYS

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The first 1,000 days of life include the period from conception to the child's first 2 years. The intrauterine period is critical to the development of the individual. Although genetics plays a crucial role, the environment, particularly nutrition, also has a decisive impact on long-term health. Any problems with malnutrition, whether by excess ("too much") or deficiency ("not enough"), can adversely affect fetal development.

The importance of epigenetics, which studies how the environment affects gene expression, modifying fetal and child development, is emphasized. The response of a developing organism to a specific change, occurring during a critical time window of the perinatal period, alters the trajectory of development itself qualitatively and quantitatively, causing permanent effects on the phenotype. This is what is meant by perinatal programming, as environmental stimuli during pregnancy can profoundly alter the development of the fetus.

Although it constitutes the life-support system of the fetus, the placenta is the least understood organ in medicine, but the study of the placenta and its functions helps to identify the molecular mechanisms that have both early and long-term effects on fetal health. Placental dysfunction is central to many pregnancy complications, such as preeclampsia (a very fearsome condition for mother and fetus, including in terms of mortality), intrauterine growth retardation, and *in utero* death. Today, for example, some child and young adult psychiatric diseases are believed to originate from exposure during fetal life to adverse factors, including hypoxia and reoxygenation. The placenta, in response to altered oxygen concentrations, is capable of releasing certain substances that can result in damage to developing neurons, at least under experimental conditions. Thus, fetal brain damage can occur not only because the amount of oxygen transported to the brain is inappropriate, but also because of the accumulation in the fetal circulation of reactive products, released by the placenta, that adversely affect the vasculature and metabolism of the brain. The precise molecular pathophysiology of placental dysfunction in these conditions is not known, and perhaps only new "omics" technologies will allow breakthroughs in this field.

Very recent evidence indicates that microplastics and nanoplastics are emerging environmental pollutants with an important impact of concern for humans. In a recent Italian study, several microplastic fragments were detected for the first time in human placenta samples: this phenomenon is called plasticenta. Microplastics and their toxic effects represent an area of growing interest, as they can interfere with crucial cellular and immune mechanisms during pregnancy. Among the consequences of environmental pollution, the effects of endocrine disruptors, smoking and other chemicals that impact fetal health should not be overlooked. Epigenetic factors also include the maternal microbiota (oral, intestinal, and vaginal) and its evolution during pregnancy. Since the microbiota is also sensitive to external influences, such as diet or oral hygiene, changes occurring in the maternal microbiota can affect fetal development, negatively but also positively.

Studies conducted on the complexity of the first 1,000 days, from the dawn of intrauterine life to the first few years of a child's life, highlight the importance of nutrition, environment, epigenetics, and prevention to ensure long-term health.

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LECT 2

EPIGENETICS DETERMINING CHILD DEVELOPMENT AND ADULT HEALTH

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Apart from the DNA "blueprint", it is actually mainly the epigenetical influences that determine both the development of the child and later the course of life, in health or illness. Specific influences from the environment, the food regimen as well as the general lifestyle shape the body, currently and what is yet to come.

These influence factors are mediated through cytokines even into the core of the cell, modulate the immune performance and change the body's metabolism. The influence of toxins forces metabolic pathways into circumventions and detours. A deprivation from essential nutrients impair proper mechanisms and enzyme functions, differing from the usual. Induced oxidative and nitrosative stress force the body into constant tension – eventually leading into an accelerated aging. Exchange processes through membranes and selective gateways stop working, if the transfer through the designated channels lacks propulsion, caused by a reduced delta (Δ) in charge difference over the sides of the membrane – but again by the concentrations and availability of nutrients in ionic form.

All of these factors are equally ubiquitous as they seem banal, yet they are all else than that. The accumulation of discreet factors modulates the physical and mental development, eventually adding up to a big bill in later years. So which factors are actually significant for the specific individual in its environment?

On the basis of implementing the S-Drive system, the indication of influence factors helps to improve and optimize therapy and consultations through a high individualization. It uses a sample of hair to indicate epigenetically relevant influences for the individual. Hence the traditional frame of (blood) lab analysis and its restrictions can be extended wider through using quantum resonance. Indicators in the intra-cellular sub-environment, connective tissue, functional systems, toxic loads, lack of nutrients and many other factors bring information into place, also prioritizing by a hierarchical order of indicators to address. By consciously omitting score values, but instead using priority and relevance for the body's functional systems, it can provide a key to solving the background and root causes for the person. And, at the same time, it can provide valuable information for prevention and optimization for the healthy individual, even professional athletes searching for performance boost. Remarkably, the system indicates sub-structure susceptibility to electromagnetic fields and frequencies. And there is an additional section on what common foods and food additives reduce the body metabolism, energy production and performance of the person, not to be confused with allergy.

Putting epigenetical influences into the picture is what modern society and applied medicine needs: detecting individual reactions that shape both the health and well-being of the person in their daily environment and the course of life. Examples hereof and the practical clinical application are shown in the lecture.

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LECT 3

EPIGENETIC FACTORS INFLUENCING LONGEVITY: A PRELIMINARY STUDY

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The feto-placental unit regulates the exchange of nutrients but also of emotions and feelings that remain imprinted in functional genes constituting the primitive epigenetic factors. If functional genes acquired during fetal development persist into the growth phase and adolescence without finding suitable stimuli for change, they may take root and contribute predominantly to the character and emotional attitude of the young adult. On the basis of these premises, preliminary results are presented in this study referring to young male adults who were subjected to S-Drive tests. In particular, signals emerged in the emotional, adrenergic, cardiovascular and immune system areas. Given the small number of data, it was not possible to draw comprehensive conclusions, but the aim was to identify possible correlations between emotional stress and alterations in the functioning of the body's support systems and in the levels of substances such as vitamins, minerals, amino acids, fatty acids, and antioxidants. The S-Drive test for individual epigenetic factors showed a deficiency in vitamin K2, whose function is linked to the prevention of brain damage and which is synthesized to counteract brain ageing and to support the connections between the cortex, diencephalon and limbic system. Production occurs through intestinal bacterial activity, again supporting the connection between intestinal and cerebral activity according to the foundations of PsychoNeuroEndocrineImmunology (PNEI). Lithium deficiency appears, which is used pharmacologically as a mood stabilizer in manic depressive syndromes, senile dementia, Alzheimer's disease and for emotional instabilities in adolescents and young individuals. Numerous studies have long highlighted the importance of alpha-linolenic acid (ALA) in the treatment of dyslexia, autism and schizophrenia. In the area of antioxidants, low levels of selenium, which is used by the body to maintain cognitive function by preventing oxidative damage to brain cells, stand out. Taurine and cysteine are also found to be deficient, thus capable of causing organic disturbances over time that could turn into chronic, disabling or even degenerative diseases. The average age of the individuals analysed and the resulting medical history suggest that most of the epigenetic factors reported by S-Drive originate from the maternal source, taking root without undergoing positive modulations during development and growth that are capable of improving the epigenetic set-up of functional genes. In order to complete the data obtained, a comparison was made with the S-Drive tests performed on the long-lived population of Ogliastra, in particular of Perdasdefogu, aged over 95 years in good health. The results homogeneously showed the absence of disruptive epigenetic factors. This finding suggests that the environment in which one is born and lives may play a predominant role in the modulation of functional genes.

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LECT 4

MITOCHONDRIAL EPIGENETIC APPROACH IN NEURODEVELOPMENTAL IMPAIRMENTS

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INTRODUCTION

Increasing scientific evidence shows that dysfunctional behaviors in children with autism spectrum disorder (ASD) or other neurodevelopmental issues are influenced by epigenetic allostatic load. This is particularly evident in relation to imbalances in the gut microbiota, with overgrowth of bacteria, viruses, molds, spores, fungi, and parasites, heavy metal overload, and difficulties in detoxifying chemicals and hydrocarbons. Additionally, improvements in children's behavioral patterns have been observed following the reduction and drainage of exposure to radiations such as radon. The presence of these epigenetic disturbances can be identified through the S-Drive test, which allows mapping of the epigenetic factors affecting the organism and mitochondrial health. Addressing these identified epigenetic/environmental factors through dietary, lifestyle, nutraceutical interventions and aromatherapy, results in a positive modulation of the child's behavior and psycho-emotional state, with reduced neuroinflammation and optimized gastrointestinal function.

AIM

The aim of our study was to investigate the response in terms of competence and well-being in children following the epigenetic corrections implemented in the family lifestyle under the guidance of the S-Drive.

MATERIALS AND METHODS

Six subjects (5 toddlers and 1 adolescent) were enrolled in the study: 4 with ASD, 1 with ADHD syndrome, and 1 with perinatal hypoxic cerebropathy. All patients were recruited at the Rivalta di Torino center dedicated to optimizing behavior and well-being in neurodevelopmental disorders (Italy). All patients underwent an S-Drive test, repeated after at last 3 months of therapy and lifestyle.

The essential oils used in these cases were:

- for the gut microbiota: *Origanum Majorana*, *Lavandula Angustifolia*, *Melaleuca Alternifolia*, *Citrus x Aurantium*, *Mentha Spicata*;
- for radiations: *Rosmarinus Officinalis*, *Origanum C.*, *Lavandula Angustifolia*;
- for chelation and antioxidant activity: *Origanum Vulgare*, *Origanum Majorana*, *Thymus Vulgaris*, *Satureja Hortensis*, *Cymbopogon Flexuosus*, *Picea Mariana*.

RESULTS

By implementing the epigenetic corrections related to lifestyle, diet, targeted nutraceuticals, drainage, and aromatherapy aimed at the identified issues, we observed an improvement in all children in physical functions such as regular bowel movements, optimal digestion, restorative sleep, and cognitive functions such as memory, concentration, and attention. There was also a reduction in dysfunctional behaviors (aggressiveness, anger, anxiety, obsessions, hyperactivity).

CONCLUSION

The results obtained correlate with data from the scientific literature, highlighting the mechanisms involving intestinal eubiosis, accumulation of toxic metals, chemicals, hydrocarbons, and radiation, and mitochondrial health (evaluated using S-Drive test) in optimizing brain behavior, immunoregulation, and neuroinflammation.

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LECT 5

MANAGING LIFE BEFORE, DURING AND AFTER PREGNANCY

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The first 1,000 days of life start from conception and continue for the first 2 essential years of postnatal life. From the formation of the zygote, which occurs through the fusion of the spermatozoon with the oocyte, all the cells and organs that will determine the entire new human being are formed. This is the period in which the adaptive capacity of the new individual is established and the main organs dedicated to resilience are set: the immune, neurological and endocrine systems.

If the fetus is female, the formation of the ovary takes place from the 8th to the 11th week after conception and at the end of this period it contains about 7 million oogonia. From this moment on, the oogonia will take the first steps of meiosis and will reduce in number to reach about 1-2 million primary oocytes, blocked in the first meiotic phase, at birth and only 700,000 at the end of the important period of the first 1,000 days of life. In practice, we can say that the biggest step towards menopause takes place even before a woman is born.

The protection of the preconception phase, pregnancy and the first 2 years of life will be very important to protect the future fertility of the new individual but also and above all to protect the correct psycho-neuro-endocrine-immunological development.

Exposure to endocrine disruptors at this stage can alter the development and differentiation of gametes, already laying the foundations for the subsequent development of gynecological abnormalities such as polycystic ovary syndrome, myomas and endometriosis, all factors that will themselves worsen future reproductive capacity.
It is really important that all health professionals who work with adolescents and pregnant women understand the importance of protecting this very important period of life.

LECT 6

INTEGRATED CLINICAL APPROACH

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During the first years of life, an integrated clinical approach can be very helpful in outlining a plan of intervention that aims at a *restitutio ad integrum* of the biological systems involved.
The S-Drive bulb test becomes important in defining a course of action, as it allows us to map out a series of dysfunctions on which to intervene in a decisive manner, respecting the interactive and systemic mode in the functioning of our organs and our various linking systems.
In fact, the S-Drive bulb test, by placing emphasis on various epigenetic disruptive factors, allows intervention at various levels, in an integrated and personalized manner, to mitigate their action and enable our organism to regain a right path to health.
Therefore, in an integrated clinical approach, factors such as detoxification, integrated nutrition, microbiota management, oxidative stress, mitochondria, and environmental impact management (electromagnetic pollution, toxic metals, chemicals, etc.) are important to guide the health of each individual at every age, respecting the natural balances and promoting a true *restitutio ad integrum* of the biological system.

LECT 7

EPIGENETIC MODULATION OF INFLAMMATION

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INTRODUCTION

Inflammation is a complex biological response sustained by the immune system and triggered by various pathogenic stimuli. In pediatrics, the main causes of inflammation include infectious pathogens (viruses, bacteria, parasites, fungi), allergens, foods, autoimmune diseases, overload of toxins and toxic metals, trauma, emotional stress, etc. The main mediators of inflammation are cytokines (IL-1, IL-6, TNF-alpha), leukotrienes, histamine, and prostaglandins. The diagnosis of inflammation is generally based on clinical data, specific laboratory tests, and targeted instrumental examinations. The main therapeutic options include medications (non-steroidal anti-inflammatory drugs, steroids, antibiotics), dietary modifications, and sometimes surgical interventions.
In this presentation, we will discuss how the S-Drive test can help to suspect and identify the underlying causes of inflammation in children and adolescents without using invasive examinations. It also enables setting up a therapy involving the elimination of any pathogenic agents, a targeted and personalized diet, and the use of specific supplements and natural products, tailored to individual needs to minimize the use of potentially toxic drugs. In all cases described, this approach has led to rapid resolution of inflammatory symptoms with stable maintenance of the result over time.

MATERIALS AND METHODS

An epigenetic S-Drive test was performed on three patients (a 10-year-old male, a 12-year-old female, and another 12-year-old female) who presented symptoms consistent with an inflammatory state, which was confirmed by the initial test performed on each of them. The first patient reported recurrent abdominal pain, often daily, for about 2 years, which had been investigated with hospitalization, blood tests, and invasive procedures (gastroscopy and colonoscopy) without identifying any objective cause for the symptom. The 12-year-old female patient complained of worsening fatigue since morning with fainting episodes without evident inflammatory symptoms over the past 6 months; the second 12-year-old female had obesity (non-responsive to personalized diet therapy) and occasional abdominal pain associated with bowel movement irregularities.
Based on the results of the S-Drive test, targeted therapy was set for each patient, including a personalized diet, phytotherapeutic products, and nutraceuticals aimed at resolving the conditions underlying the identified inflammatory state. The

patients were monitored with serial S-Drive tests (every 4-5 months) to track altered indicators and reassess therapeutic choices if necessary.

The S-Drive test, performed using hair bulbs, provides an epigenetic overview of an individual's health and wellness by analyzing bio-information from the hair follicles. This technology captures resonance information from the hair bulb, reflecting the body's interaction with its environment and underlying metabolic processes.

The clinical interpretations from the S-Drive test include several key parameters:

- nutritional and diet optimization: the test assesses the individual's current nutritional status and identifies deficiencies or excesses in vitamins, minerals, fatty acids, and antioxidants, helping tailor dietary recommendations to optimize health;
- personal immune stressors: it identifies potential immune system challenges or stressors, such as exposure to toxins, allergens, or infections that can influence overall health and inflammation levels;
- electromagnetic interference: it evaluates the impact of electromagnetic fields from electronic devices and other sources, suggesting ways to mitigate their potential negative effects on health;
- metabolic and environmental factors: it analyzes various metabolic processes and environmental influences affecting the body's epigenetic expression, such as exposure to pollutants, chemicals, and lifestyle factors.

Thanks to the S-Drive test, we can identify specific markers related to inflammatory states, particularly:

- vitamins and minerals: vitamin D, essential for immune system modulation; vitamin C, important for immune function and as an antioxidant, its deficiency can impair immune response and increase oxidative stress; magnesium, crucial for reducing oxidative stress and inflammation, its deficiency is associated with increased inflammatory reactions;
- essential fatty acids: omega-3 possess anti-inflammatory properties, low levels can lead to chronic inflammation and an increased risk of inflammatory diseases; omega-6: while essential, an excess of omega-6 compared to omega-3 may promotes inflammation;
- antioxidants: glutathione, a potent antioxidant that protects cells from oxidative damage, its deficiency can lead to increased oxidative stress and inflammation;
- amino acids: cysteine is a precursor of glutathione, essential for synthesizing this antioxidant, its deficiency can reduce the body's ability to counteract inflammation; glutamine, important for maintaining the integrity of the intestinal barrier, its deficiency can lead to intestinal and systemic inflammation; histamine, a crucial mediator of inflammation, particularly related to connective tissue status.

By correlating the various markers and their presence across different test domains, we can derive therapeutic considerations and options for rebalancing: oxidative stress markers (an increase in free radicals that can damage cells and tissues, promoting chronic inflammation); omega-3 and omega-6 balance (an imbalanced ratio may suggest the need for omega-3 supplementation to reduce inflammation); vitamin and mineral deficiencies (identifying and correcting these deficiencies can help modulate the body's inflammatory response and improve immune function).

RESULTS

In all cases examined and treated according to the clinical evidence of the S-Drive test, a significant outcome in terms of remission of symptoms and maintenance of outcome was achieved.

CONCLUSIONS

Inflammation in pediatric age can have multiple causes that are not always identifiable with conventional diagnostic methods; the S-Drive test has proven to be a valuable tool for detecting epigenetic factors interfering with well-being and identifying inflammation markers that help better understand the clinical picture. This approach allows for personalized therapy, recommending a targeted nutritional plan and monitoring the clinical evolution with serial tests (every 4-5 months) to maintain the achieved result over time.

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LECT 8

NUTRACEUTICALS AND PHYSIOLOGICAL OXYGEN MODULATION

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Mitochondrial diseases are inherited diseases that affect energy metabolism and mainly affect the nervous system, heart, skeleton, and muscles and the energy metabolism of cells. Clinically, they present extremely variably as they can affect any organ or system in our body. Most frequently, symptoms of mitochondrial disease involve energy-intensive tissues, such as the central nervous system, heart, and skeletal muscle. Mitochondrial diseases can begin in all age groups, from childhood to youth to adulthood. When taken together, there are over 200 different forms; the incidence is about 1:5,000 live births.

Nutraceutical support in mitochondrial function is important. The antioxidant and antiproliferative activity of the supplement Cellfood™ (CF) has been documented in recent years by several experimental evidences both *in vitro* and *in vivo*. Early *in vitro* studies demonstrated that CF has high antioxidant capacity and is able to protect both biomolecules (glutathione and DNA) and cells (erythrocytes and lymphocytes) from reactive oxygen species (ROS)-induced oxidative damage [1]. At the same time, studies on cultured endothelial cells have shown that CF enables increased oxygen consumption and ATP production, thereby promoting mitochondrial oxidative activity [2]. Overall, CF is thus able to modulate oxygen at the cellular level, allowing all possible benefits to be derived from cellular oxygenation without intervening in the oxidative processes associated with it. Such *in vitro* evidence has also been confirmed by some *in vivo* studies. Indeed, CF supplementation has been shown to be effective in reducing serum levels of ROS in subjects at risk of oxidative stress such as athletes, smokers, and the overweight. In patients with osteopenia, CF supplementation significantly reduced serum levels of oxidized lipoproteins, which are involved in the occurrence of atheromatous plaque. Similarly, in patients with neurodegenerative diseases, CF treatment significantly reduced serum levels of ROS with concomitant increase in plasma antioxidant capacity and glutathione levels [3]. The high antioxidant action of CF and its ability to promote mitochondrial oxidative activity could also underlie the clinical benefits observed in both fibromyalgia patients and professional athletes. Indeed, in fibromyalgia patients, treatment with CF significantly alleviates pain symptoms, muscle weakness, fatigue upon awakening, and in general complaints associated with reduced mood [4]. In professional marathon runners and cyclists, CF increases oxygen availability with improved cardio-respiratory and physical performance, with benefits also in the adaptation process during the training period. Further *in vitro* studies have shown that CF also possesses an effective antiproliferative action against numerous cancer cells in culture such as leukemia cells and mesothelioma cells, melanoma, colon, lung, bladder and breast carcinoma. In fact, it has been observed that CF induces cell death by apoptosis through two main mechanisms: on the one hand, it alters cellular glycolytic metabolism by reducing the expression of the hypoxic factor HIF-1α and the membrane receptor for glucose GLUT-1 [5]; on the other hand, it acts on the survival mechanisms of the tumor cell by reducing the expression of key factors such as Akt, Bcl-2, and c-myc and by promoting the expression of cell cycle regulators such as p53, p21, and p27 [6].

Confirming what has been observed *in vitro*, recent *in vivo* studies in animal models (data being published) have shown that pretreatment with CF prevents tumor mass formation in 70% of mice injected with tumorigenic mesothelioma cells. At the same time, administration of CF to mesothelioma mice also improves the effect of radiotherapy in combination with chemotherapy treatment (cisplatin + pemetrexed) by reducing the expression of hypoxic factor HIF-1α.

In conclusion, scientific studies to date suggest that CF may be a valuable adjuvant in the prevention and treatment of various physiological and pathological conditions related to mitochondrial dysfunction especially before pregnancy and in children in the first 100 and 2,000 days of life; further studies have demonstrated the nutraceutical's action on modulating oxidative stress, from cellular aging to neurodegeneration and cancer. Indeed, due to its antioxidant, oxygenating, and pro-apoptotic properties, CF could be a good candidate in pre-primary and primary prevention and support in cancer prevention and provide important clinical benefits in combination with standard antineoplastic therapy. Further studies are ongoing both *in vitro*

and *in vivo*; more confirmations are desirable for both *in vitro* and *in vivo* prevention and integrated clinical support.

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