Fifth Stromboli Conference on Aging and Cancer

June 13-19, 2010
Sirenetta Park Hotel
Stromboli Island, Aeolian Islands Messina, Sicily, Italy

"The Primeval Life-Generating Molecules. Therapeutic and Aging-Reversing Properties"

Interbion Foundation for
Basic Biomedical Research,
Gordola, Switzerland (est. 1980)

"The Primeval Life-Generating Molecules. Therapeutic and Aging-Reversing Properties"

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Fifth Stromboli Conference on Aging and Cancer
13-19 June, 2010

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DAILY SCIENTIFIC PROGRAM
(June 14-June 18)

Eight scientific sessions:
morning 8.30-12.30AM;
afternoon 3.30-7.30PM
Each session includes 4 speakers (35-40min talk and 10min discussion) 1, 20min - coffee break

June 14, 8.30-8.45 AM
Wellcome greetings (W. Pierpaoli)
The everlasting island

June 14, morning session 8.45-12.30 AM
Pineal gland, melatonin and aging
Chairman: Lesnikov Vladimir

8.45-9.25: Bartsch Christian:
Longitudinal Melatonin Production in Female Laboratory Rats During 1997-2006: Possible Modulatory Effects of Changing Solar Activity
9.25-10.10: Diaz Lopez Beatriz:
Ovarian ageing: melatonin regulation of the cytometric and endocrine pattern

10.10-10.30 Coffee break

10.30-11.40: Stehle Jörg:
Physiological significance of the pineal gland and its hormone melatonin
11.40-12.30: Tresguerres Jesus:
Beneficial effect of chronic melatonin treatment on several physiological parameters of old male and female Wistar rats

June 14, afternoon session, 3.30-7.30PM
New key molecules expecting their physiologic role!
Chairman: Bartsch Christian

3.30-4.20: Dizhevskaya Antonina:
Natural dipeptides as perspective class of anti-cataract drugs: molecular mechanism of inhibition lens BL-crystallin aggregation

4.20-5.10: Kamath Jayesh:
Thyrotropin-releasing hormone (TRH), cancer-related fatigue & the immune system
5.10-5.30 Coffee break

5.30-6.40: Luo LuGuang:
Thyrotropin Releasing Hormone (TRH) promotes insulin producing cell proliferation
6.40-7.30: Pierpaoli Walter:
Aging-reversing properties of Thyrotropic Releasing Hormone (TRH)

June 15, morning session, 8.30-12.30AM
New and "old" molecules for aging-delaying and aging-reversing interventions
Chairman: Anisimov Vladimir

8.30-9.20: Birkmayer George:
Coenzyme 1 (NADH): the only real fuel for cellular energy with a scientfically proven anti-aging effect
9.20-10.10: Carruthers Malcolm:
Testosterone deficiency syndrome: cellular and molecular mechanism of androgen action

10.10-10.30: Coffee break

10.30-11.20: Khokhlov Alexander:
Does aging need its own program, or the program of development is quite sufficient for it? Stationary cell cultures as a tool for search of anti-aging factors
11.20-12.10: Lesnikov Vladimir:
Cytoprotective and immunomodulatory effects of transferrins: relevance to aging

12.10-12.30: General discussion

June 15, afternoon session, 3.30-7.30PM
Origin, nature, prevention and treatment of neoplastic processes
Chairman: Lahiri Debomoy

3.30-4.20: Anisimov Vladimir:
Light at night-induced circadian disruption, cancer and aging
4.20-5.10: Hill Steven:
Age related decline in melatonin and its MT1 receptor levels are associated with decreased sensitivity to melatonin and enhanced mammary tumor growth

5.10-5.30: Coffee break

5.30-6.10: Lissoni Paolo:
Cancer as a main aging factor in humans. Reversal of cancer-induced aging processes on metabolic and immune reactions by pineal hormones other than melatonin. The fundamental role of 5-methoxytryptamine
6.10-7.00: Pierpaoli Walter:
Our endogenous "pineal clock" and cancer. Cancer and non-cancer. Strategies for early detection, prevention and cure of neoplastic processes

7.00-7.30: General discussion

June 16, morning session, 8.30-12.30
Neurodegenerative diseases - Part 1
Chairman: Jovanova-Nesic Katica

8.30-9.20: Boldyrev Alexander:
Molecular mechanisms of homocysteine toxicity for nervous and immune systems
9.20-10.10: Jacovak Hrvoje:
MetallothioneinS I+II expression and tissue metals kinetics during chronic relapsing experimental autoimmune encephalomyelitis in rats

10-10-10.30: Coffee break

10.30-11.20: Marchetti Bianca:
Reactive Astrocytes are Key Players in Nigrostriatal Dopaminergic Neurorepair/ Rege-neration in the MPTP-mouse Model of Parkinson's Disease

11.20-12.00: Sambamurti Kumar:
Metabolites that induce neurodegeneration as therapeutic targets

12.00-12.30: General discussion

June 16, afternoon
FREE: BOAT TRIP, CLIMB TO THE VOLCANO, SIGHTSEEING, SHOPPING, SWIMMING, RELAXING, HISTORICAL SWEET MEDITERRANEAN DO-NOTHING

June 17, morning session, 8.30-12.30
Neurodegenerative diseases-Part 2
Chairman: Marchetti Bianca

8.30-9.20: Jovanova-Nesic Katica:
Aluminum Excitotoxicity and Innate Neuroautoimmunity: The Role of the Expression of CD32 and ICAM-1 in the Rat Brain
9.20-10.10: V. M. Mikhelson:
Telomere Shortening is a sole mechanism of aging in mammals

10.10.10.30: Coffee break

10.30-11.10: Rybakova Antonina:
Non-receptor and receptor mediated oxidative stress in murine cerebellum neurons and neuroblastoma both accompanied by phosphorylation of MAP (ERK1/2) kinase
11.10-12.00: Radosevic-Stasic Biserka:
Morphogenetic properties of endoplasmic reticulum-resident heat shock protein GP96

12.00-12.30 General discussion

June 17, afternoon session, 8.30.12.30
Mechanisms of reproduction, immunity and aging
Chairman: Kamat Jayesh

3.30-4.20: Arutjunyan Alexander:
The Ability of Melatonin and Pineal Gland

Peptides to correct the Impairment of Reproductive Cycles in Rats
4.20-5.10: Clayton Paul:
The innate immune system in the management of infection and cancer

5.10-5.30: Coffee break

5.30-6.20: Kay Marguerite:
Immunoglobulin and antibody interventions during aging; theoretical and therapeutic considerations of damage reversal
6.20-7.00: Mocchegiani Eugenio:
Plasticity of neuroendocrine-thymus interactions during ontogeny and ageing: Role of zinc and arginine for healthy ageing and longevity

7.00-7.30: General discussion

June 18, morning session, 8.30-12.30
Preventative medicine, regeneration, repair, nutrition strategies
Chairman: Clayton Paul

8.30-9.20: Coll Sanchez Francisco Javier:
Marine therapy and its healing properties
9.20-10.10: Di Nicola Valerio:
Self-Repair in Degenerative Joint Disease

10.10-10.30: Coffee break

10.30-11.10: Micans Philip:
Aortic wave velocity, a measurement of the stiffness index (SI) of arteries and the results of certain supplements that appear to improve the SI
11.10-12.00: Rossi Pier Luigi:
From calories to molecules. The role of carbohydrates and AGEs in arteriosclerosis

12.00-12.30: General discussion

June 18, short afternoon session 3.30-5.30PM
General discussion and workshops
Chairman: Novera H. Spector

Pierpaoli Walter:
Remembering Branislav Jankovic, Bill Regelson, Vladimir Dilman, Don McCann, Nicola Fabris
Spector, Novera:
The Fifth Stromboli Cocktail

Gala dinner and farewell party (9 until 12PM)
Aeolian Music and Dancing: informal dress
SEMEL IN ANNO, LICET INSANIRE!

LIST OF SPEAKERS

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"Light at night-induced circadian disruption, cancer and aging"

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"The Ability of Melatonin and Pineal Gland Peptides to correct the Impairment of Reproductive Cycles in Rats"

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"Seasonal and solar cycle-mediated modulation of pineal melatonin production in the laboratory rat"

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"NADH, a scientifically proven anti-aging substance"

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"Molecular mechanisms of homocysteine toxicity for nervous and immune systems"

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"Testosterone deficiency syndrome: cellular and molecular mechanism of androgen action"

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"The innate immune system in the management of infection and cancer"

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"Marine therapy and its healing properties"

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"Self-Repair in Degenerative Joint Disease"

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"Ovarian aging: melatonin regulation of the cytometric and endocrine evolutive pattern"

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"Histidine dipeptides with anti-cataract activity inhibit the ultra-violet-induced aggregation of beta- L-christalline"

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"Age related decline in melatonin and its MT1 receptor levels are associated with decreased sensitivity to melatonin and enhanced mammary tumor growth"

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"MetallothioneinS I+II expression and tissue metals kinetics during chronic relapsing experimental autoimmune encephalo-myelitis in rats"

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"Aluminum Excitotoxicity and Innate Neuroautoimmunity: The Role of the Expression of CD32 and ICAM-1 in the Rat Brain"

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"TRH, Cancer-related Fatigue and the Immune System"

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"Immunoglobulin and antibody interventions during aging; theoretical and therapeutic considerations of damage reversal"

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"Does aging need its own program, or the program of development is quite sufficient for it? Stationary cell cultures as a tool for search of anti-aging factors"

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"Role of Epigenetics, and Dietary Intervention in the Aging-related Disorders"

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"Cytoprotective and immunomodulatory effects of transferrins: relevance to aging"

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"Cancer as a main aging factor in humans. Reversal of cancer-induced aging processes on metabolic and immune reactions by pineal hormones other than melatonin. The fundamental role of 5-methoxytryptamine"

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"TRH promotes insulin -producing cell proliferation"

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"Reactive Astrocytes are Key Players in Nigrostriatal Dopaminergic Neurorepair/Regeneration in the MPTP-mouse Model of Parkinson's Disease"

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"Aortic wave velocity, a measurement of the stiffness index (SI) of arteries and the results of certain supplements that appear to improve the SI"

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*"Plasticity of neuroendocrine-thymus interactions during ontogeny and ageing:
Role of zinc and arginine for healthy ageing and longevity"*

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1) *"Our endogenous "pineal clock" and cancer. Cancer and non-cancer. Strategies for early detection, prevention and cure of neoplastic processes"*
2) *"Aging-reversing activity of thyrotropin releasing hormone (TRH)"*

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"Morphogenetic properties of endoplasmic reticulum-resident heat shock protein GP96"

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"Effect of histidine containing dipeptides on cell cycle and signaling in neuroblastoma cell lines"

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"From calories to molecules. The role of carbohydrates and AGEs in arteriosclerosis"

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"Metabolites that induce neurodegeneration as therapeutic targets"

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"Science and the aging Stromboli cocktail: the never-ending quest continues!"

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"Physiological significance of the pineal gland and its hormone melatonin"

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"Effect of chronic melatonin administration on various physiological parameters in the aging rat"

ABSTRACT

Light at night-induced circadian disruption, cancer and aging

Vladimir N. Anisimov[1], Irina A. Vinogradova[2], Andrey V. Bukalev[2], Andrei V. Panchenko[1], Irina G. Popovich[1], Anna V. Semenchenko[1], Mark A. Zabezhinski[1]

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Light-at-night has become an increasing and essential part of modern lifestyle and leads to a number of health problems, including excess of body mass index, cardiovascular diseases, diabetes and cancer. The International Agency for Research on Cancer (IARC) Working Group concluded that "shift-work that involves circadian disruption is probably carcinogenic to humans" (Group 2A) [Straif et al., Lancet Oncol. 2007; 8: 1065-1066]. According to the circadian disruption hypothesis, light-at-night might disrupt the endogenous circadian rhythm, and specifically suppress nocturnal production of pineal hormone melatonin and its secretion in the blood. We evaluated the effect of various light/dark regimens on the survival, life span and spontaneous and chemical carcinogenesis in rodents. Exposure to constant illumination was followed by accelerate aging and tumorigenesis in female CBA and transgenic HER-2/neu mice. Male and female rats were subdivided into 4 groups and kept at various light/dark regimens: standard 12:12 light/dark (LD); natural lighting of the North-West of Russia (NL); constant light (LL), and constant darkness (DD) since the age of 25 days until natural death. We found that exposure to NL and LL regimens accelerated switch-off of the estrous function (in females), development of metabolic syndrome and spontaneous tumorigenesis, shortened life span both in male and females rats as compared to the standard LD regimen.

Melatonin given in nocturnal drinking water prevented the adverse effect of the constant illumination (LL) and natural light (NL) regimens on the homeostasis, life span and tumor development both in mice and rats. The exposure to the LL regimen accelerated colon carcinogenesis induced by 1,2-dimethylhydrazine (DMH) in rats whereas the treatment with melatonin alleviated the effect of LL. The maintenance of rats at the DD regimen also inhibited DMH-induced carcinogenesis. The LL regimen accelerated whereas the DD regimen inhibits both mammary carcinogenesis induced by N-nitrosomethylurea and transplacental carcinogenesis induced by N-nitrosoethylurea in rats. These observations allow recommend to use melatonin for cancer prevention in groups of humans at risk of light pollution.

References

Anisimov V.N. Light pollution, reproductive function and cancer risk. Neuro Endocrinol. Lett. 2006; 27: 35-52.

Straif K., Baan R., Grosse Y. et al. Carcinogenicity of shift-work, painting, and fire-fighting. Lancet Oncol. 2007; 8:1065-1066.

Vinogradova I.A., Anisimov V.N., Bukalev A.V., Semenchenko A.V., Zabezhinski M.A. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats. Aging. 2009; 1: 855-865.

ABSTRACT

The Ability of Melatonin and Pineal Gland Peptides to correct the Impairment of Reproductive Cycles in Rats

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Catecholamines have been found by us and other investigators to play an important role in the hypothalamic regulation of the secretion of gonadotropin-releasing hormone [1, 2]. The present study is dedicated to melatonin and the pineal gland peptides (epithalamine and epitalon) correcting influence on the diurnal dynamics of norepinephrine (NE) in the medial preoptic area (MPA) and of dopamine (DA) in the median eminence with arcuate nuclei (ME-Arc) disturbed by single administration of 1,2-dimethylhydrazine (DMH) in female rats. It has been found that melatonin is able to cure a number of breaches of the hypothalamic component of reproduction caused by the neurotoxic xenobiotic DMH. It has been shown that experiments with DMH administration can be used as an animal model of female reproductive system premature aging. The investigation of epithalamine (polypeptide preparation from bovine pineal gland) effect on circadian rhythms disturbed by the neurotoxic compound DMH has shown a recovery of diurnal dynamics of NE in MPA. In addition, NE was found to decrease from 9:30 till 11 o'clock, the circadian time (CT), which was typical of control animals. Epitalon (Ala-Glu-Asp-Gly) proved to be more effective in ME-Arc. This peptide prevents the xenobiotic caused disturbance of DA diurnal rhythm, keeping this metabolite low at 5 o'clock (CT) with its having increased by 11 o'clock (CT). The data obtained suggest that pineal gland plays an important role in the circadian signal normalization needed for gonadoliberin surge on the day of proestrus. Melatonin and peptides of the pineal gland can be considered as effective protectors of female reproductive system from xenobiotics and premature aging.

[1] *Arutjunyan A.V., Kerkeshko G.O., Anisimov V.N., Stepanov M.G., Prokopenko V.M., Pozdeyev N.V., Korenevsky A.V. Disturbances of diurnal rhythms of biogenic amines contents in hypothalamic nuclei as an evidence dimethylhydrazine // Neuroendocr. Lett.* ***22(4)****, 229-237, 2001.*
[2] *Goldman J.M., Murr A.S., Buckalew A.R., Cooper R.L. Suppression of the steroid-primed luteinizing hormone surge in the female rat by sodium dimethyldithiocarbamate: relationship to hypothalamic catecholamines and GnRH neuronal activation // Toxic. Sci.* ***104(1)****, 107-112 (2008).*

ABSTRACT

Longitudinal Melatonin Production in Female Laboratory Rats During 1997-2006: Possible Modulatory Effects of Changing Solar Activity

Bartsch H.[1], Mecke D.[2], Vollrath L.[3], Probst. H.[2], Küpper H.[1], Seebald E.[1], Herget I.[4], Lehmann H.[7], Peschke E.[5], Salewski L.[6], Stehle T.[2], Bartsch C.[1]

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Earlier we reported that the nocturnal production of melatonin (estimated by the urinary excretion of 6-sulfatoxymelatonin, aMT6s) displayed circannual rhythms in two inbred strains of laboratory rats (female F344 Fischer and BDII/Han) with peaks occurring in summer [1,2] and hypothesized that seasonal changes of the horizontal component H of the geomagnetic field may act as *zeitgeber*[1]. To better understand this phenomenon, four experiments were performed with female Sprague-Dawley (SD) rats kept in the same climatized rooms observing them for 18-20 months each and collecting overnight urine (19-7 hrs CEST) at monthly intervals from two months of age onwards.

In **experiment I (n=12: 1997-1999)** aMT6s increased from winter to summer by 30%. The cosinor analysis revealed a rhythm with a phase-length of 24 months and a peak in July 1998. The rhythm-adjusted mean (mesor) amounted to 359 ng/12hrs and the amplitude was 28 ng/12 hrs. In **experiment II (n=12; 1999-2001)** aMT6s showed a winter/summer increase by 40%. A rhythm was detected with a phase-length of 18 months showing a peak in September 2000. Compared to exp. I the mesor was elevated by 28% and the amplitude by 68%. In **experiment III (n=30; 2003-2004)** aMT6s showed a 20% winter-summer increment. A circannual rhythm with a peak in April/May was found. The mesor was 13% higher than in exp. I but the amplitude was depleted by 14%. Also in **experiment IV (n=15; 2005-2006)** aMT6s showed a slight increase of 15% from winter to summer. A low-amplitude rhythm of 24 months' phase-length with a peak in June 2006 resulted. The mesor was comparable to exp. I but the amplitude was lowered by 36%.

These results show that female SD-rats until two years of age show elevated melatonin production during summer- resp. spring-time. This supports our initial hypothesis regarding a seasonal *zeitgeber* function of H [1]. It is, however, apparent that longitudinal melatonin rhythms displayed considerable amplitude variations in the four consecutive experiments performed under highly standardized conditions. To account for this, it has to be considered that the geomagnetic field is disturbed by solar activity undergoing typical changes throughout the 11-years' sunspot cycle. Incidentally, the experiments paralleled solar cycle 23 (1996-2008): exps. I and II (1997-2001) were carried out during the phase of ascending solar activity which peaked during 2000-2 whereas exps. III and IV (2002-6) were performed during declining activity. In the course of exps. I and II the longitudinal mesor and particularly the amplitude of aMT6s increased (+28% resp. 68%) whereas during exps. III and IV (2002-6) the amplitude declined by 14% resp. 36% compared to exp. I. This indicates that solar activity may modulate longitudinal melatonin secretion patterns. It appears that summer peaks of melatonin are more pronounced in and around peak solar activity of the 11-years' cycle and that increasing geomagnetic disturbances within the ascending limb facilitate seasonal melatonin rhythmicity. This assumption is supported by our earlier studies [1,2] which showed high circannual aMT6s-amplitudes

which were carried out during the peak-phase of solar cycle 22 (1990-2). We assume that the observed longitudinal modulations of pineal activity may affect aging and cancer as well as the responsiveness of laboratory animals to experimental manipulations.

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ABSTRACT

Coenzyme 1 (NADH): the only real fuel for cellular energy with a scientfically proven anti-aging effect

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Coenzyme-1 (N.A.D.H.) is one of the most important coenzyme catalyzing more than a thousand of metabolic reactions in the human body, the most important of which is the production of ATP (Adenosin-Tri-Phosphate).
The more ATP energy a cell has available the better it can function and the longer it can live. It has been shown with isolated heart cells that NADH can increase ATP in these cells by 30%[1]. The vitality and lifespan of these heart cells were also increased by NADH. This heart cell system allows to test other coenzymes and substances for which an energy increasing effect has been claimed.
NADH as biological form of hydrogen is a very sensitive substance which degrades rapidly. The author succeeded in stabilizing NADH and transposing it into a tablet form in which NADH is stable for at least 2 years. Based on the patent protection of this product numerous GCP studies have been performed in the U.S. as well as in Europe. In an FDA approved double-blind placebo controlled study it was found that NADH leads to an improvement of certain cognitive functions in patients with Alzheimer dementia[2]. Another FDA approved double blind study with patients suffering from CFS (Chronic Fatigue Syndrome) revealed more than 80% of the patients were relieved from their fatigue after a 6 month treatment period with 10 mg NADH per day. In a further study the effect of NADH on cognitive performance of healthy middle aged individuals after sleep deprivation for 24 hours was tested at Cornell University.
Subjects taking 20 mg of NADH did not only better in terms of cognitive performance than the placebo subjects but did more than 3 times better than the same subjects at base line, after a full night sleep[3]. In other words, NADH enhances cognitive performance in healthy individuals and due to its energy-increasing effect for the brain it may prevent MCI (Mild Cognitive Impairment) as well as Alzheimer dementia. As most cancer cells exhibit an ATP deficiency and NADH can increase ATP energy in cells this coenzyme was given to cancer patients in an open label trial. 17 prostate cancer patients with pathologically proven carcinoma have been cured in 3 to 5 months with a daily dose of 40 mg NADH. A number of patients with mammary carcinoma and small cell lung cancer have been cured in between 6 months with the same daily dose of NADH[4]. More than 60 cancer patients have been treated so far with NADH most of them are disease free or show no tumour progression. The increase in physical and mental energy was reported from all the cancer patients taking NADH.
The mechanism of action of NADH is based on the elevation of the intracellular ATP. NADH plays also an important role in cell and DNA repair.
Hence NADH can act as an agent preventing cancer, Alzheier dementia and for many ailments particular for those based on mitochondrial dysfunctions.

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ABSTRACT

Molecular mechanisms of homocysteine toxicity in nervous and immune systems

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Hyperhomocysteinemia is a known risk factor of secondary stroke and heart attack as well as a feature accompanying development of human neurodegenerations. In the paper, the data are presented that main target for homocysteine is glutamate receptors of NMDA class which expression is characteristic of both neuronal and immune competent cells [1,2]. Homocysteine is found to activate NMDA receptors thus inducing calcium entry into cytoplasm and accumulation of reactive oxygen species (ROS). The following step is phosphorylation of Erk1/2 kinase which may result in activation of apoptotic process. Activation of NMDA receptors by homocysteine in T cells results in stimulation of cytokine synthesis (IFN-γ and TNF-α)[3], whereas neutrophyls respond to this stimulus by activation of respiratory burst[4]. In both cases, only activated cells are sensitive to homocysteine because activation of immune cells is accompanied with expression of NMDA receptors. Using two different models spinal cord injury and inflammation centre creation we demonstrated that immune cells can express NMDA receptors after *in* vivo activation[5]. In a model of prenatal hyperhomocysteinemia in rats[6] we have found that neuropeptide carnosine (antioxidant and immune modulator) protects animals against homocysteine toxicity with no change of the blood homocysteine levels. Based on these data, carnosine was tested as an additional drug to treat human being diseases accompanied by increased levels of blood homocysteine. In the case of both chronic brain ischemia and Parkinson disease carnosine was found to increase in efficiency of treatment being used in combination with basic therapy[7]. Carnosine effect has been directed rather to protection of tissues from excitotoxic effect of homocysteine than to increased metabolism of this toxin.

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Key words: Hyperhomocysteinemia, NMDA receptors, immune cells, carnosine
Izheier dementia and for many ailments particular for those based on mitochondrial dysfunctions.

ABSTRACT

Testosterone Deficiency Syndrome: cellular and molecular mechanism of androgen action

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Introduction. Central to the diagnosis and treatment of testosterone deficiency syndrome in the adult male is the remarkable paradox that there is a very poor correlation between the characteristic symptoms and levels of serum androgens.
Aim. Because androgen deficiency can be associated with severe symptomatology, as well as diverse conditions such as coronary heart disease, diabetes, and metabolic syndrome, the aim was to present an evidence-based working hypothesis to resolve this confusing clinical paradox.
Methods. A review of the possible mechanisms in testosterone deficiency syndrome was carried out, and a hypothesis to explain this paradox and associated problems in the diagnosis and clinical management of androgen deficiency was established on the basis of a review of the literature.
Main Outcome Measures. The mechanisms by which androgen deficiency could arise were studied at five different
levels:
1. Impaired androgen synthesis or regulation.
2. Increased androgen binding.
3. Reduced tissue responsiveness.
4. Decreased androgen receptor activity.
5. Impaired transcription and translation.

Results. As with insulin in maturity onset diabetes mellitus, there can be both insufficient production and variable degrees of resistance to the action of androgens operating at several levels in the body simultaneously, with these factors becoming progressively worse with aging, adverse lifestyle, other disease processes, and a wide range of medications.
Conclusions. Using this model, androgen deficiency can be redefined as an absolute or relative deficiency of androgens or their metabolites according to the needs of that individual at that time in his life. There are important ways in which the considerations raised by this hypothesis affect the etiology, terminology, diagnosis, and treatment of androgen-deficient states.

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ABSTRACT

The innate immune system in the management of infection and cancer

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The innate immune system is a fertile hunting ground for novel therapies, two of which will be discussed in this paper.

1. Novel antibiotic system.
The use of bactericidal antibiotics inevitably drives antibiotic resistance across all classes of antibiotics and pathogens. While others have focused on the genomic mining of soil microbes, we looked for novel antibiotics in the innate immune system. This highly effective anti-microbial system comprises multiple physical, humoral and cellular components: we identified the ferro-protein lactoperoxidase (LPO) as a potential therapeutic device. Present in many secretions including airway and gut surface fluids, LPO produces hypothiocyannous (HOSCN) and hypothiocyanate (OSCN) ions with broad spectrum activity against gram-positive and -negative bacteria, HIV-1 and other viruses, moulds, yeasts, mycoplasma and protozoa (ie Fweja et al '08), via three mechanisms. They inhibit bacterial glycolysis; they inhibit bacterial nicotinamide adenine dinucleotide (NADH)/nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reactions; and they oxidise bacterial and viral sulphydril groups. We used LPO derived from cow's milk to generate OSCN and HOSCN ions in vitro, and administered these in a multi-centre clinical trial of over 250 subjects with diverse infections. A cure rate in excess of 80% was recorded. LPO operates in close conjunction with the Cystic Fibrosis Transmembrane Regulator (CTFR) Cl- channel, which conducts / supplies LPO's second substrate, SCN- (Pedemonte et al '07). A follow-up trial in CF is logical, as the application of effector ions bypasses the key lesion in CF; and is planned.

2. Novel anti-cancer strategy
Innate immune cells such as tumoricidal granulocytes are critically involved in endogenous immunosurveillance and in the therapeutic application of anti-cancer MAb's. The high incidence of cancer and the low cost/benefit ratios of MAb's suggest that innate cellular defence is frequently compromised; and this is supported by data on dietary shift and dramatic changes in the incidence of both cancer and allergy in the period 1850 to 2000. These suggest that naturally occurring CR-3 agonists should be valuable anti-cancer adjuncts; this has now been shown in pre-clinical (Salvador et al '08) and more recently in clinical models.

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ABSTRACT

Marine therapy and its healing properties

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Anti-aging is the way to avoid the aging of the cells in human.The best way to avoid aging is to find the correct way to feed and nurture the cell so it can react before any endogenous or exogenous aggressions of the XXI century.
The American scientist J. Craig Venter after harvesting seawater in different places in the oceans has demonstrated that NEW life continues to appear in the Sea. New genes that do not belong to any known specie and new protein families appear in Venter's filters. Sea is the origin of Life.
The Biotechnological department at Alicante's University has discover that human cells live longer in seawater that in any other isotonic solution.
René Quinton, a humanist of the XX century, developed and based a therapeutic on this. The used of a natural milieu, the isotonic seawater, to reactivate the cells in the organism. The Marine Therapy is not based in acting against something, but rather in the balance of the body which means being healthy. Cells correctly fed will know how to react against any aggression by themselves.
The importance of having all the elements of the periodic table available to the cell in its 100% bioavailability form only can be given by seawater. Works of Professor Maurice Aubert, from the International Sea University of Nice, proved that the elements in ionic dispersion are completely bioavailable by humans thanks to the action of the phytoplankton.
The analysis done by Alicante University, proved the presence of 78 natural elements and in similar proportion to our organic liquids. This was the big discovery of René Quinton: the identity between our internal milieu and the isotonic seawater.
Water and elements go through a specific path described by Roderrick MacKinnon and Peter Agre, Nobel Price of Chemistry in 2003, whom taught us the existence of ionic and hydro receptors in the cell membrane. Through the cytoskeleton and nucleoporines' microtubules, the elements get to the nucleus where the genes are. The elements will allow the reading, transcription and expression of the genes through the metabolic cascades. The presence of the polyelements is vital to activate these cascades.
The retrospective on René Quinton's works teaches us how isotonic seawater is the most complete natural solution that the organism needs for its nutrition. The worldwide spreading of the Marine Therapy has allowed us to obtain results in pathologies as wide as pathologies of the skin, digestives or inflammatory in places like in Southeast Asia.

"L'eau de mer, milieu organique" René Quinton, 1904

"Le Dispensaire Marin" Jean Jarricot, 1921

"Estudio in Vitro para evaluar la activad inmunomoduladora de la solución isotónica e hipertónica Quinton en células humanas de sangre periférica"

II Congreso Europeo de Inmunología, Berlín.
GRUPO DE INVESTIGACIÓN DE INMUNOLOGÍA
Departamento de Biotecnología, Universidad de Alicante, 2009

ABSTRACT

Self-repair in degenerative joint disease

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This study presents a method for treating and structurally improving articulations affected by Degenerative Joint Disease (DJD). The focus of this analysis is on two groups of patients (pts). The first one composed of over-eighties while the second group was of 45 to 55 year old pts. The first group had high surgical risk and both had been non-responders to currently adopted conservative therapies.
Scholars like Davis, Filatov and Cerletti have been studying and using the regenerative properties of placenta, amnios and other non vital tissues since the early '900's. These pioneering studies have opened a new track for tissue renewal. More recently, the new biological knowledge about extra cellular nucleic acids, growth factors (GF)-as by-products of trauma response- and heat shock proteins (Hsp) has helped research even further.
Building on those experiences, we have developed a regenerative gel obtained with distressed, processed blood, Polydeoxyribonucleotides (Pdrn) and a thickening substance. The objective was to stimulate the local innate stem-cells with our gel in order induce tissue repair.
From 2003 until 2009 we treated 948 pts. As mentioned, the first group was composed of 86 ultra-octogenarian pts with severe osteoarthritis (OA) of the hip and/or knee, and the second group was composed of 90 young pts (around fifty year old) affected by the same disease.
Treated patients have been clinically and radiologically evaluated with a follow-up of 6 to 48 months. Results show a statistically significant improvement in terms of pain and joint mobility, sometimes coupled with a clear radiological improvement. Follow-up shows encouraging data in terms of clinical stability over time. During the study we encountered virtually no side effects, adverse reactions or toxicity.
Currently the pharmacological treatment of DJD is palliative. It has toxicity and side effects. Patients that can be operated conclude their trial with a prosthesis followed by a long rehabilitation period.
This study suggests a new methodological approach and treatment of DJD based on tissue regeneration and restoration resulting in clinical resolution.

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ABSTRACT

Ovarian ageing: melatonin regulation of the cytometric and endocrine pattern

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Introduction: A beneficial effect of melatonin treatment on the neuroendocrine-reproductive axis during ageing was previously observed (Díaz el al., 2000). Specific melatonin receptors have been described in rat ovaries (Cohen et al., 1978) or in ovarian follicular fluid (Brzezinski et al., 1987), suggesting a direct effect of this pineal hormone on ovarian function. We attempted to investigate the effect of exogenous melatonin administration on ovarian function during ageing.

Material and Methods: Young cyclic (3-month-old), middle-aged preacyclic (13-month-old), and old acyclic (22-month-old) female Wistar control and melatonin treated (150 _g/100 g BW, s.c) for two months, were used. Ovaries were removed and frozen at -80ºC to determine the cell cycle by flow citometry; the stereological study of the ovary, volume and oocytes number; and the p53 and Ki67 proteins by immunohistochemistry. It is known that immunohistochemical detection of the antigen Ki67 and p53 protein was associated with the prognosis of cancer (Fridman et al., 2003). Endocrine function was evaluated by the plasma estradiol E_2 levels, measured by radioimmunoassay (RIA).

Results: Cell cycle: the highest percentage of cells were in G0/G1 gap in both control and melatonin treated groups, but this percentage is significantly reduced in ovaries from melatonin treated female rats compared to control for the three different reproductive stages studied. The percentage of cells in S-phase increased significantly ($p<0.0001$), ($p<0.001$) when cyclic and acyclic female rats were treated with melatonin. The percentage in G2-M gap significantly increased in ovaries from melatonin treated young rats as compared to ovaries from control rats.

Stereological study: the ovarian cellular volume was affected by melatonin treatment at the middle-aged preacyclic stage, showing significantly higher ($P<0.05$) volume mm^3 in the ovaries from melatonin treated rats at this age compared to the control group. The oocytes number was not modified by melatonin treatment.

Immunohistochemical study: there was no significant labelling in p53 nor in Ki67 ovarian tissues at the three different ages for either control or melatonin treated rats.

Endocrine study: melatonin resulted in higher E_2 levels at the middle-aged stage.

Conclusions: Melatonin increased the DNA synthesis capacity (S-phase) of the ovarian cells at young and old ages, and improved the ovarian function at middle age. Melatonin did not produce deleterious side effects.

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ABSTRACT

Natural Dipeptides as Perspective Class of Anti-cataract Drugs: Molecular Mechanism of Inhibition Lens β_L-Crystallin Aggregation

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The effect of histidine-containing dipeptides (carnosine and N-acetylcarnosine) on preventing and treating the cataract of a various aetiology had been demonstrated in many studies in vivo (1-3). The exact molecular mechanisms of dipeptide action are practically unclarified. Cataract has been recently attributed to conformational diseases due to association of aggregation of the lens structure proteins with cataract pathogenesis. The effect of histidine-containing dipeptides on the UV-induced β_L-crystallin aggregation has been studied *in-vitro*. The dipeptides used were of various hydrophobicity. It was first demonstrated that N-acetylcarnosine (NAC) and anserine (10-40 mM) strongly inhibited UV-induced aggregation of β_L-crystallin, while carnosine exerted no effect. The positive correlation of anti-aggregation activity for dipeptides used and their hydrophobicity was obtained. It was revealed that NAC and anserine inhibited the initial stages of the protein photochemical damage. The decrease of protein aggregate size was detected by dynamic light scattering in the presence of NAC and anserine. Moreover, UV irradiation of β_L-crystallin solution significantly increased the number of protein carbonyl groups - a well-known protein oxidation marker. At the same time addition of the histidine-containing dipeptides to the protein solution before UV irradiation did not influence the carbonyl group content in the oxidized β_L-crystallin. It was supposed that NAC and anserine inhibited β_L-crystallin aggregation via formation of protein-dipeptides complex that prevented macromolecular conformational changes and ensuing protein aggregation.

Key words: cataract, β_L-crystallin, histidine-containing dipeptides, protein aggregation.

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ABSTRACT

Age Related Decline in Melatonin and its MT1 Receptor are Associated with Decreased Sensitivity to Melatonin and Enhanced Mammary Tumor Growth

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The pineal hormone melatonin (MLT) has potent anti-breast cancer activity and its actions are heavily mediated via the MT1 receptor and subsequent modulation of down-stream signaling pathways including cAMP/PKA, Erk/MAPK, p38, and Ca^{++}/Calmodulin. Also, via the MT1 pathway, MLT can repress the transcriptional activity of some mitogenic nuclear receptors including ERα, GR, and RORv, while potentiating the activity of other receptors (RARα and RXRα involved in differentiation, anti-proliferation, and apoptosis (1). A review of the literature supports the view that MLT, via its MT1 receptor, can suppress all phases of breast cancer including initiation, promotion, and progression of breast cancer (2). Serum MLT levels have been reported to diminish significantly by the 5th and 6th decades of life as the incidence of breast cancer increases (3). Given MLT's anti-cancer activity, we hypothesized that the age-related decline in pineal MLT production leads to enhanced breast cancer development and growth as women age. This study was designed to determine if the growth of tissue-isolated mammary tumors in young (2 months), adult (12 months), and old (20 months) female Buffalo rats relates to the age-related changes in MLT and its MT1 receptor. Serum MLT levels were measured in both the light and dark phases. A significant 29% decrease in the peak nighttime serum MLT levels was observed in the adult and old rats (75% decrease) as compared to young rats. In young rats, the nighttime pineal gland MLT content exceeded daytime levels by 19-fold compared to a 7-fold increase in old mice. Also, a significantly diminished nighttime and early morning level of the MT1 receptor was observed in uteri from old rats compared to young and adult rats. Analysis of growth rates in transplanted, tissue-isolated, N-nitroso-n-methyl-urea (NMU)-induced mammary tumors showed a significant increase in old rats as compared to young or adult rats. Additionally, diminished response to the growth suppressive action of exogenous MLT was noted in old rats, such that tumor growth was suppressed by only 33% compared to 48% and 66% in adult and young rats, respectively. This decrease in tumor response to exogenous MLT correlates with reduced expression of the MT1 receptor in old as compared to young and adult rats. These data suggest that enhanced mammary tumor growth is associated with old age and that diminished levels of MLT and its MT1 receptor during old age reduce tumor sensitivity to the inhibitory actions of exogenously MLT.

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ABSTRACT

Metallothioneins I+II expression and tissue metals kinetics during chronic relapsing experimental autoimmune encephalomyelitis in rats

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Metallothioneins (MTs) are small, cysteine-rich proteins that have been implicated in various forms of stress providing cytoprotective action against oxidative injury, DNA damage and apoptosis. Owing to their high affinity for physiological metals, such as zinc and copper MTs are also critical components of multiple regulatory proteins involved in cell growth and multiplication, as well as in the maintenance of immune homeostasis, affecting the functions of immune cells, TLR signaling, upregulation of co-stimulatory molecules on antigen-presenting cells (APC) and the production of pro-inflammatory cytokines. Therefore, their expression may be induced through several response elements in the MT gene promoter: 1) metal response elements, which are activated by the metal-responsive transcription factor-1 after zinc occupancy, 2) glucocorticoid responsive elements activated by stress, 3) elements activated by signal transducers and activators of transcription proteins through cytokine signaling and 4) the antioxidant (or electrophile) response element (ARE) activated in response to redox status.

The extensive data show that these proteins confer a protective effect also within the mammalian CNS, where the MT I+II expression dramatically increases in response to many types of CNS and spinal cord (SC) injury or ischemia, as well as in senescence and in several neurodegenerative and autoimmune diseases.

To obtain an insight into the changes of MT-trace metal circuit during the development of an autoimmune disease, in this study we correlated the expression of MT I+II in the brain, SC and liver with total zinc and copper content in these organs, during clinically different stages of chronic relapsing (CR) experimental autoimmune encephalomyelitis (EAE): 1) in early, asymptomatic phase (on the 7th post-immunization day; 2) during periods of attacks (on the 12th and the 22nd day), and 3) during the period of remissions of EAE (on the 18th and the 28th day). Disease was induced in the genetically susceptible DA rats by subcutaneous injection of encephalitogen (bovine brain homogenate in CFA). Rats in the control groups were treated only with CFA. MTs I+II and tissue metals were evaluated by immunocytochemistry and by inductively coupled plasma spectrometry, respectively. Additionally, in the asymptomatic stage of EAE the free intracellular Zn^{2+} content in the brain and SC were visualized by Zinquin (a selective Zn^{2+} fluorophore).

The data revealed an early upregulation of MTs and free Zn^{2+} content in the brain and SC in preclinical phase of disease and their marked overexpression during both attacks at sites of invasion of myelin-reactive T cells into CNS and their reactivation on local APC (on endothelial cells, ventricular subependyma, microglia/macrophages and astroglial cells around the ventricle walls and blood vessels), as well as in the molecular layer of cerebellum, in subgranular layer of gyrus dentatus, and on several neurons and oligodendrocytes in SC. Simultaneously, increased the content of free Zn^{2+} at these sites and the total Zn^{2+} content in the cervical SC. Furthermore, during attacks in the liver markedly arose the expression of MT I+II and tissue concentrations of total zinc and copper.

The data point to neuroprotective role of MTs and to important regulatory role hepatic MTs in pathogenesis of EAE (Supported by grant 0621341-1337 from Croatian Ministry of Science).