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Drug Discovery and Design

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GENERAL INFORMATION

REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS INTERNATIONAL EDITION

The Journal aims to promote optimum drug therapy by providing original papers and review articles covering important aspects of clinical and applied Pharmacology and Therapeutics. The focus of the Journal comprises drug evaluation reviews, which provide a detailed focus on different properties, i.e. dosage, toxicology, drugs interactions and a place in therapy of both newer and established drugs. Other Review Articles offer state-of-the-art literature surveys covering broader topics. Practical Therapeutics Articles and Leading Articles provide recommendations for specific situations of connections or emerging areas, respectively.

The Journal publishes, in special issues, papers presented at:
- the *Conferences with International Participation Medicinal Chemistry: Drug Discovery and Design organized by the Departments of Chemistry and Pharmacy of the University of Patras, Hellas*
- the *Panhellenic Congresses of Pharmacology organized by the Hellenic Society of Pharmacology*

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INSTRUCTIONS TO AUTHORS

English is the preferred language for all papers. However, papers in French, German or other European languages can also be submitted, provided they are accompanied by an English summary.

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Acknowledgements and References

Manuscripts: These should mention, on the first page, the *Title*, *Author(s)* and the *Name of the Institution* at which the work was done. The complete *address* of the author, including Postal area code number, should be given under the rubric *Send reprint requests to*. Papers should follow the general form: *Introduction, Materials and Methods, Results, Discussion* and *References*. Drugs must be referred to by their generic or chemical name, but may be identified by trade name in parenthesis or o footnote. All papers should be submitted in duplicate.

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Letter from the Guest Editor

In this 19th Medicinal Chemistry Anniversary Conference in Amaliada, we celebrate 20 years of operation since the beginning of the Program in 1998. The Conference has been under the Auspices of H.E. the President of the Hellenic Republic Mr Prokopios Pavlopoulos who has honoured the program with his Presence in the Official Opening.

It was a great honour for our Conference to host again Nobel Laureate Harald zur Hausen and Professor Vasso Apostolopoulos. Their contribution to Science and Society is unmesurable and they constitute an Example and Light for our students.Furethermore, the program has attracted the interest of world leading scientists among them five Nobel Laureates.

The program has been a success story for the University of Patras. It has been worldwide recognized for excellent research and for high quality education and training offered to our students. I am happy for the participation of many of them visiting us from other Universities and countries where they serve as Ambassadors of Greece.

The vision and final goal of this course was to establish a high-tech research program aiming to translate basic research to applied to the benefit of Research and Society. This program resulted in highly trained scientists, innovations and ground breaking research. More than 400 students have graduated from the program with successful careers in Greece and abroad.

On behalf of the Post Graduate Program I wish to express my gratitude to all who have contributed to the great success of this program, in particular esteemed invited scientists, colleague teachers, our graduate students, collaborators in research. I would like also to thank Elizabeth Diamantopoulou, Biology Student and Elias Theodoropoulos, Economics Student, for their great input in editing this Issue.

Above all we thank heartfully the Editorial Board of Review of Clinical Pharmacology and Pharmacokinetics. In particular we thank Journal Editors Prof. S. T. Plessas and Dr C. T. Plessas for invitation and for providing the suitable and high-standard forum through which important finding of this research will come available to the scientific community.

The Guest Editor
John Matsoukas
Professor of Chemistry

Issue Devoted to Papers Presented at the

19th Medicinal Chemistry Conference

Municipality of Ancient Ilida, Amaliada

September 22, 2018

Drug Discovery, Design & Development

The Conference was held

Under the Auspices of H.E.
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REVIEW CLINICAL PHARMACOLOGY AND
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Speech of His Excellency the President of the Hellenic Republic, Mr. Prokopios Pavlopoulos in the Opening of the 19th Medicinal Chemistry Conference

Conference and Cultural Centre of the Municipality of Ilida
Amaliada Sept 22, 2018

It is a great honor for me to attend, as a President of the Hellenic Republic the 19th conference of "Medicinal Chemistry", which is co-organised by Ilida Municipality, the Graduate Program "Medicinal Chemistry" of the University of Patras, the International Olympic Academy and by the Association of Greek Chemists. My sincere congratulations to all of you, for this bright initiative. And allow me to say that I am particularly pleased, as this Conference is being held at the new, ultramodern, Conference and Cultural Center of the Municipality of Ilida, which I just inaugurated and represents a true jewel for the City of Amaliada and for the whole surrounding area. A truly cultural centre, which the Municipality of Ilida should have acquired long ago, considering its long history of Hellenique Culture, from the ancient to the modern era. I. In first place, and as I am sure that I express all attendee's feelings, I shall praise the personality of Professor Giannis Matsoukas, President of the Organizing Committee of the Conference, for his internationally recognized research work in Chemistry as well as for his great educational contribution to the University of Patras, of which he himself was a bright graduate. He is serving the Excellence in practice, an Academic frame which is predominantly democratic, as it aims at promoting the abilities of the best individuals and practices, regardless of social, financial or other criteria. At this point, I have to point out that our educational system -with its problems and deficiencies- has been, during the entire post-war period, an important tool for facilitating mobility. Surely, the educational system achieved this only when -and so far - it served the principle of Excellence. II. Reading the names of the Nobel Laureates who are members of the Honorary Organising Committee, as well as the names of those who participate in the Conference by submitting a contribution, suffices, for anyone to perceive the international recognition of the "Medical Chemistry" postgraduate program, which today celebrates the 20 years of its life. And I should note that the lead speaker and guest of honor at the Conference and at Ilida Municipality is the distinguished Greek-Australian Professor of Immunology of the University of Victoria in Australia , Dr. Vasso Apostolopoulos, who will speak about the progress of her research on cancer and multiple sclerosis treatment. I. While having a great appreciation for all the speakers, without exception, let me, nevertheless, draw your attention to a great personality of modern Medical Science, which brightens with his presence this Conference. A. The Professor of the Medical School of Heidelberg University, Harald zur Hausen, who has been awarded the Nobel prize in Medicine and Physiology for his research on immunotherapy of cervical cancer, who participates to this conference as a speaker. Millions of women world-wide, do not develop this type of cancer because of the vaccine developed based on his research; therefore, Professor zu Hausen is fairly considered as a Benefactor of Mankind. B. Furthermore, each of us realizes,

without being a medical doctor, the huge importance of the research, which Professor zur Hausen is conducting the past few years, on the causes of the development of cancer, as it is an essential prerequisite for its prevention. The emphasis given by Professor zur Hausen on the prevention of cancer, before the equally essential development of treatment methods, must be treated carefully by all component for the protection of human health public bodies, at a national as well as at an international level. C. We honor the great Philhellene Professor zur Hausen today, for one more important reason. This is related to his support to Greece, even during the recent period of financial crisis, which posed a threat on the existence and continuance of the scientific and technological research in Greece, at the high level that had been acquired the past decades. Professor zur Hausen, cosigning scientific "Support Greece Petition" with his Nobel Prize Laureates colleagues, at every opportunity, attempted to inform the International Science Community as well as the Political Leadership for the aforementioned danger, in order to accomplish the support of Excellence in the scientific and technological research being conducted by the Greek Universities and Research Institutes. A great action, which had the same goal, was the publishing in the magazine "Science", in the issue of the 25th May 2012, of a letter signed by himself on behalf of 22 top scientists and titled "Support for Greece". 1. This letter had been previously sent to Martin Schulz, the former President of the European Parliament, to Herman Van Rompuy, the former President of the European Council, as well as to Jose Manuel Barroso, the former President of the European Commission. This letter made such an impression to the International Science Community, that even the Nobel Laureate James D. Watson -who in cooperation with Crick and Wilkins discovered the DNA structure, and who is part of the Honorary Organizing Committee of this Conference- sent a letter to Herman Van Rompuy, on the 15th June 2012, stating that he stands together with those colleagues who, led by Professor zur Hausen, published this text in "Science". Meanwhile, he suggests, at the concluding sentence of his letter, that action needs to be taken soon, so that Science and Centers of Excellence can be supported, in order for development and prosperity to exist in Greece. 3. The information presented above underline the great offering of Professor zur Hausen to Greece, for which, we thank him. I remind you that the Hellenic Nation paid tribute to Professor zur Hausen for his offering, by awarding him the Award "Order of Phoenix". IV. In conclusion, I express my admiration to those who study, like you do, the biological and chemical structure of this unique and complex species, called Human, citing an extract from the article "Biological Clocks", published by the remarkable Austrian biologist, biochemist and violinist, Gottfried Schatz, in "Neue Zürcher Zeitung": "I often wonder, which biological clock makes us feel that the Viennese waltz owes its rhythmical verve to the subtle time shift to the second meter of its tone? Which biological clock has Rainer Maria Rilke listened to when he was writing "Sonnets to Orpheus"? And which internal metronome revealed to the orchestra manager Wilhelm Furtwangler the barely noticeable rhythmic fluctuations, with which he managed -as no one else did- to enliven an Adagio? These clocks count split seconds, and simultaneously the pulse of hours. How much I would like to know to which one of the hundreds of billions of nerve cells of my body I owe the priceless gift of these magical clocks! Because these clocks give meaning to my life and make it beautiful". With these thoughts, I congratulate you for the organization of a Conference of actually global scope and I wish every success to your Conference and research projects.

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Anticancer Research is the Best Therapy

Harald zur Hausen
University of Heidelberg, Germany
Nobel Laureate

Απόσπασμα από την ομιλία του καθηγητή Harald zur Hausen στο 19ο Συνέδριο Ιατρικής Χημείας

Cervical cancer kills thousands of women annually, and nearly 85% of these deaths occur in developing nations, where it is the leading cause of cancer deaths in women. Disparities of health and poverty play a large role in this high mortality rate. Whereas routine Papanicolaou and human papillomavirus (HPV) testing has dramatically reduced cervical cancer deaths in Western nations, without proper infrastructure, facilities, and medical training, the rates of cervical cancer in developing nations will remain high. Studies on HPV DNA testing and the low-technology method of “screen and treat” are promising. In addition, reducing the cost and increasing the availability of HPV vaccines in developing nations brings hope and promise to the next generation of women.

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Immune modulation in Medical Research: What have we achieved.

Vasso Apostolopoulos
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The basis of T cell stimulation is via the specific interaction of an immunogenic peptide in complex with MHC by a T cell receptor. Other co-stimulatory molecules such as CD80, CD86 on antigen presenting cells, are recognised by T cells via CD28 and CTLA-4 which results in T cell activation. In recent years the identification of checkpoint markers such as PD-L1, PD-L2 on antigen presenting cells, epithelial cells etc and their interaction with PD-1 on activated T cells results in apoptosis of T cells and immune escape mechanisms, in the case of cancer [1] .The role of checkpoint markers in a range of disorders including autoimmune disorders, inflammatory disorders and cancer are being studied with a plethora of information being published in the last 1-2 years. In addition, peptide alterations of T cell epitopes with 1-2 amino acid mutations can have drastic effects on the outcome of this recognition. Such peptides are termed, altered peptide ligands that can act as modulators of immune responses as they have the ability to downregulate or upregulate responses [2, 3] . Over the last 20 years, there has also been an emphasis on carriers, adjuvants and delivery systems to modulate immunity in vitro, in vivo in animal models of disease and in human clinical trials [4, 5] . With this information we are well placed to develop novel immune modulators for disease and we have been successful in developing novel immune modulators for cancer and autoimmune disorders which were discussed in the presentation [6-8].

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IL-27 responsiveness in dendritic cells is essential for antigen-specific tolerance against ongoing CNS autoimmunity

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Multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) are inflammatory demyelinating diseases of the CNS, resulting from an autoimmune reaction against myelin antigens. In the CNS, infiltrating autoreactive Th1/Th17 (CD4+) cells, CD8+ T cells, macrophages/dendritic cells (DCs), mast cells, as well as activated microglia, produce proinflammatory cytokines IFN-γ, IL-17, IL-23, TNF-α and GM-CSF, and promote cell-mediated immunity. Conversely, tolerogenic APCs, Th2, Tregs and regulatory B cells that produce immunoregulatory cytokines IL-4, IL-13, IL-10, and TGF-β may be protective. Antigen (Ag)-specific immune tolerance can be induced by administration of Ags via various routes, including oral, nasal and intravenous (i.v.) Auto-Ag-induced peripheral tolerance is achieved through the suppression of self-reactive lymphocytes and stimulation of tolerogenic DCs, regulatory T (Treg) cells and production of anti-inflammatory cytokines. IL-27 has been shown to induce tolerogenic DCs and Treg cells in vivo and in vitro, however, it is unclear whether IL-27 is important for tolerance induction. In this context, we aimed to study the role of IL-27 in induction of peripheral tolerance. MOG35-55-immunized wild-type and IL-27R (WSX-1) knockout mice were intravenously injected with MOG35-55 peptide after onset of EAE and the clinical development of disease and immunological parameters were analyzed. Although antigen administration reduced disease severity in wild-type mice, treatment was ineffective in WSX-1-/- mice. Disease amelioration correlated with reduced infiltration of cytokine-producing CD4+ T cells and diminished antigen-specific cellular response. Similar results were observed in oral tolerance approaches. IL-27 signaling in T cells was not necessary for tolerance but dendritic cells emerged as an important target of IL-27 signaling to induce tolerance. Further mechanistic studies showed that IL-27-dependent tolerance relied on cooperation of distinct subsets of spleen dendritic cells with the ability to induce T cell-derived IL-27, IL-10 and IFN-γ. Together, these data demonstrate an essential role of IL-27 responsiveness of DCs in antigen-induced peripheral tolerance against ongoing CNS autoimmunity, and perhaps in other autoimmune disorders as well.

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Multiple Sclerosis research in Greece: targeting clinical trials

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This communication is dedicated to Dr. Elizabeth Matsoukas who was the inspiration of the research

Myelin based research for Multiple Sclerosis (MS) in Greece was triggered by Dr. Elisabeth Matsoukas, a Biologist, who has been struck by the disease. That happened in 1982 at the age of 29. Following her diagnosis, she dedicated her life to promote research into MS. Her PhD dissertation from the National research Institute in Athens identified and evaluated myelin epitopes implicated in the pathogenesis of the disease. In particular she studied epitopes of the Myelin Basic Protein (MBP). In 1994 it was decided to include in our research program at the University of Patras the design, synthesis and development of mimetics and conjugates of MBP epitopes as potential immunotherapeutics to prevent and treat disease.Thefirst experimental allergicen cephalomyelitis (EAE) experiment was run in 1994 at the University of Pennsylvania in Professor Mohamad Rostami's lab (currently Chairman of the Department of Immunology in Thomas Jefferson University, USA and elected President of the Philadelphia Neurological Society).

Further experiments were carried out using the guinea pig epitope MBP72-85 as suggested by Elisabeth[1]. The search for new therapies was part of her curiosity to determine the mechanisms of the disease. That first EAE experiment in Pennsylvania was successful which paved the way for further research to identify new peptide immunomodulators, which resulted in research based on the myelin epitopes MPB83-99, MOG33-55 and PLP139-155. A multi-institutional and multi-disciplinary consortium was established by Professor John Matsoukas and Professor Vasso Apostolopoulos in 1999, and distinguished scientists in top Universities and Institutions worldwide (Europe, USA, Canada, Australia) participated in this research. This approach, resulted in novel findings and potential new immunotherapeutics against MS. Professor Vasso Apostolopoulos (from the Austin Research Institute; currently at Deputy Vice-Chancellor, Research at Victoria University Australia),who had developed a novel antigen delivery system against cancer, applied her insights into MS research. The delivery system used which specifically targets dendritic cells was able to modulate immune responses from pro-inflammatory to anti-inflammatory and protection and reversal of EAE in animal models[2-8]. After 25 years of research and successful toxicology studies we are ready for a human phase I clinical trial using a GMP (good manufacturing practice) conjugate; the clinical trial will be conducted by Victoria University, Australia. [9-10]

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Protein Misfolding Simulation Tools in Drug Discovery

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Introduction: The majority of protein molecules must be stable and folded into defined three dimensional structures to perform their functional activity. However, cells usually contain correctly folded proteins together with a multitude of conformational states. These misfolded proteins are prone to forming toxic aggregates, including soluble oligomers and fibrillar amyloid deposits, being the underlying cause of several severe and incurable age-related disorders linked with neurodegeneration such as Alzheimer's disease [1, 2, 3]. To ensure protein homeostasis (or proteostasis) and avert protein aggregation, cells have developed a wide-ranging network including molecular chaperones and other factors [4]. These exquisite machineries degrade or either refold correctly misfolded proteins, but they tend to decay during aging, thus enabling the development of aggregate deposition diseases [5]. Knowledge of the impact of protein folding has led to an explosion of work in protein structure determination and prediction, further facilitating drug design. Molecular experimental methods mostly used for the determination of a protein's structure are time consuming and high-priced. Thus, a remarkably wide range of computational prediction methods that can precisely, rapidly and automatically categorize unknown protein sequences into definite fold classes is required. Bioinformatics and computational biology have made remarkable progress in recognition of protein structures and a variety of computational prediction methods has been generated [6]. Our study focusses on the current knowledge about the etiology of many protein folding diseases with the use of high – throughput simulation technologies.

Protein fold recognition through simulation tools: The elucidation of how amino acid sequences lead to correctly folded and fully functional proteins in cells remains one of the greatest challenges in science. This understanding will have a significant effect in various fields of biology and medicine and will mostly lead to the rational design strategies to generate new pharmaceutical proteins and drug molecules. In consequence, the determination of the fold category of a protein, a process that is called fold recognition, is fundamental revealing the tertiary structure of proteins. Traditional experimental methods that are used for the determination of a protein structure are X-ray crystallography and nuclear magnetic resonance spectroscopy. Since the completion of the Human Genome Project, a vast number of protein sequences is rapidly generated by next-generation sequencing techniques. Although many of these sequences are structurally characterized using experimental methods, a cumulative gap is created between the

structurally determined sequences and uncharacterized ones. Therefore, the development of computational methods for rapid and precise determination of protein folds is obligatory.

Consequently, many simulation tools for the accurate prediction of protein structures have been recently developed offering an alternative approach to the demanding, time consuming and high-priced experimental methods [7]. Protein fold recognition is studied with methods that can be largely categorized into the following classes:

(1) de novo methods. This series of approaches require long computational time and numerous sources, while they can only be effectively applied in small proteins.

(2) template-based methods which are used for the determination of protein structures comparing proteins that are evolutionary related. These methods are considered very effective for the construction of theoretical models of protein structures and

(3) template-free methods, that are based mainly on amino acid sequences to build the model and predict a protein's structure precisely.

Conclusion: Constantly there is active research to define the mechanisms by which disease-associated proteins misfold and create aggregates causing cellular toxicity. These processes are the hallmark of many incurable pathologies such as Alzheimer's disease. Continued progress in our ability to determine precise protein structure will utilize rational design strategies that will result in discovering novel pharmaceutical molecules. Compared with the traditional experimental methods, computational methods present many advantages such as the demonstration of robust, accurate and consistent performance, they can be applied in large-scale protein fold recognition. Furthermore, they can efficiently address the intrinsic restrictions of experimental methods, that is, their being labor intensive and expensive.

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Experimental models in Multiple Sclerosis and neurophysiology: Preclinical studies of citrullinated MBP analogues in Wistar rats

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Multiple sclerosis (MS) is a disease of the Central Nervous System (CNS). It begins when activated peripheral immune cells such as T-cells, B-cells macrophages and microglia, infiltrate through the disrupted Blood-Brain-Barrier into the CNS .It generally strikes at an early age, most often the early adult years. Its most frequent symptoms include numbness, impaired vision, loss of balance, weakness, bladder dysfunction and psychological changes. The disease can wax and wane for up to 30 years, but in perhaps half of all cases it steadily progresses to severe disability and premature death. MS is an autoimmune disease triggered by CNS-specific CD4+ T lymphocytes. Candidate autoantigens include constituents of the myelin sheath, such as Myelin Bacic Protein (MBP), Proteolipid Protein (PLP) and Myelin Oligodendrocyte Glycoprotein (MOG). Although the pathology of MS remains unclear, there is evidence that T-cells recognizing encephalitogeni epitopes of myelin, such as MBP, play a pathogenic role in the induction of MS. Studies have shown that T-cells responses in patients are associated with the recognition of the 81-105 region of MBP.T -cell recognition of this region of MBP has also been shown in healthy individuals, although at relatively low precursor frequencies. The pathogenetic role of autoimmune T-cells recognizing encephalitogenic epitopes of MBP has also been noted in Experimental Autoimmune Encephalomyelitis (EAE), the animal model of MS. EAE represents an invaluable in vivo system for the evaluation of therapeutic approaches. EAE is induced in susceptible animals by immunodominant epitopes of the myelin sheath. Similar clinical and histopathological features to MS can be induced in susceptible mouse strains by immunization of myelin components. In this study a model of EAE is developed by giving citrullinated MBP 83-99, a molecule which has the ability to induce the production of highly toxic cytokines to Central Nervous System (CNS).The goal of this study was to investigate the possibility of occurrence clinical symptoms and to study electrophysiologically the effects of this EAE model on wistar rats. Initial clinical results were produced over a period of about one month and complete paralysis of the rat tail was observed, while the electrophysiological experiments showed a prosynaptic energy potential reduction of up to 50% compared to control rats. The peaks in the waveform are the population energy potential of mausoleum prosynaptic axons. The picture shows their displacement right in relation to the onset of irritation, due to the increase in the distance of the recording electrode from the excitation electrode. [1-4].

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The role of Human Papilloma Virus in Oropharyngeal Carcinoma

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Human papilloma virus (HPV) has been identified as a cause of the increasing prevalence of oropharyngeal squamous cell cancer (OPSCC) worldwide. The aim of this review is to provide an overview of HPV associated oropharyngeal cancer. Emphasis is placed on the epidemiology, diagnosis, treatment, prognosis and prevention of the disease.Review of the recent literature (2008–2018) using the keywords oropharyngeal cancer, head and neck cancer and human papilloma virus. The worldwide incidence of HPV-positive oropharyngeal cancer has dramatically increased in the last thirty years. The rise in incidence is more pronounced in younger, non-smoking men in Western countries. The prognosis of HPV related OPSCC is favourable compared to non-HPV related tumours. This has led to a trend in adopting more conservative medical and surgical treatment paradigms. HPV vaccination is currently offered to both males and female adolescents as a measure to prevent disease occurrence in later adult life. The emergence of HPV and minimally invasive techniques has led clinicians to reconsider the management of OPSCC. The advent of HPV vaccination should be adopted worldwide to reduce disease burden.

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Design and synthesis of peptide-drug conjugates selectively targeting cancer cells

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Cancer is the second leading cause of death affecting nearly one in two people, and the appearance of new cases is projected to rise by >70% by 2030. To effectively combat the menace of cancer, a variety of strategies have been exploited. Among them, the development of peptide–drug conjugates (PDCs) is considered as an inextricable part of this armamentarium and is continuously explored as a viable approach to target malignant tumors. The general architecture of PDCs consists of three building blocks: the tumor-homing peptide, the cytotoxic agent and the biodegradable connecting linker.

Our aim is to provide a spherical perspective on the basic principles governing PDCs, as also the methodology to construct them. We aim to offer basic and integral knowledge on the rational design towards the construction of PDCs through analyzing each building block, as also to highlight the overall progress of this rapidly growing field. Therefore, we focus on several intriguing examples of PDCs from our laboratory research and we address possible difficulties that may emerge during the synthesis of PDCs, as also report ways to overcome them.

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Patient X-ray dose in brain perfusion Computed Tomography imaging

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Brain CT Perfusion (CTP) is an X-ray imaging technique for the assessment of brain tissue perfusion, especially in acute stroke patients. The aim of this study is the evaluation of the radiation dose to patients during a comprehensive brain CT prescription protocol (CPP) consisting of an unenhanced brain CT, a brain CT angiography and a CTP scan. Eighteen patients were studied using an 80-slice CT system, with an iterative reconstruction algorithm. The volume Computed Tomography Dose Index (CTDIvol) and Dose Length Product (DLP) were recorded. The calculation of the effective dose (ED) was accomplished using the DLP values. For the CTP examinations, the CTDIvol ranged from 116.0 to 134.8 mGy, with the mean value 119.5 mGy. The DLP ranged from 463.9 to 539.2 mGy·cm, with the mean value 478 mGy·cm. For the CPP, the total ED ranged from 3.31 to 5.07 mSv, with the mean value 4.37 mSv. These values are lower than the values reported in corresponding studies, including studies utilizing CT systems with more slices. The results highlight the necessity and importance of the harmonic collaboration between the radiologists and the medical physicists, leading to enhanced utilization of the system used.

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Rational design of flavonoids based prodrugs triggered by alkaline phosphatase for treatment of metastatic prostate cancer

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Prostate cancer consists the second most common cancer in men, while the current standard treatment modality has a good prognosis. Although, when it metastasizes in different sites becomes lethal. Bone metastasis is the most common metastatic site along with lymph nodes. Once a patient has been diagnosed with bone cancer, the prognosis is unfortunately extremely poor and life expectancy is very as short. Several factors are contributed to the proliferation of prostate metastatic cancer cells. Alkaline phosphatase (ALP) is a group of isoenzyme widespread in mammalian tissues and responsible for the hydrolysis of monophosphate ester groups from various protein and non-protein substrates1. The elevated levels of ALP are often associated with many malignasies, such as breast and prostate cancer2, thus it is used commonly as a diagnostic marker. Flavonoids have served as a rich reservoir for the generation of potential drugs as possess a rich pharmacological profile, including anti-inflammatory, anti-angiogenic and anti-carcinogenic properties in vitro and in vivo3, 4. Despite their plentiful benefits on human health, their application in medicine is limited due to their poor aqueous solubility and low bioavailability, as the numerous phenol groups incommode the transportation through the lipophilic cell membrane5, 6. In order to enhance their pharmacological profile and to achieve both selective delivery and release to tumor cells, we report the synthesis and the biological evaluation of one flavone based phosphate prodrug. The cytotoxicity of the prodrug was evaluated in different metastatic and non- metastatic tumor cells overexpressing different levels of ALP. Finally, we studied and determined the interaction between apigenin and alkaline phosphatase utilizing an array of techniques including fluorimetry, STD NMR and tr NOESY NMR.

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Monitoring bone reconstruction in fractures of femurs using Raman Spectroscopy

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The reconstruction of animal models' femur in the vicinity of a fracture was monitored using Raman spectroscopy. For this purpose male Wistar rats were used, which simultaneously underwent a surgery of artificial fracture of the right femur. The animals were divided into 4 groups, based on the post-operative week they were sacrificed (6, 8, 10 and 12). The left femur was used as a control for each animal. Visual assessment of the femurs revealed, in accordance with literature, that fracture follows healing in three different ways: a) the "fracture line" which progressively disappears, b) the "soft callus" created in the vicinity of the fracture and c) the "hard callus" in the same area. Raman spectra were collected from the periosteum of all bones scanning a wide area on both sides of the fracture point as well as from the endosteum of fracture cross section. *The intensities of the characteristic vibrations of the main bone constituents, bioapatite and collagen, were measured and* the following Raman metrics were calculated: Mineral to Matrix Ratio, Carbonate to Phosphate Ratio, Crystallinity and Cross Linking Ratio.

Comparison between the four groups, in order to track the progression of bone regeneration in time, showed that there was a slight improvement of the Raman ratios for the bones with the "fracture line" and the "hard callus" from week 6 to week 8. However, these types of healing bones failed to reach the quality of the normally grown bone, even after 12 weeks of healing.The newly formed bony tissue was characterized by limited calcification and low crystallinity, being, thus, more fragile than a healthy one. Furthermore, the increased crosslinking of the collagen network, reduced its elasticity and made it more rigid. The "soft callus", on the other hand, showed absolutely no sign of progress over time. Finally, the Raman metrics from the endosteum at the cross section of the fracture were significantly improved compared to values for the periosteum, for all types of fracture healing. This suggested that the healing proceeds from endosteum, where increased activity is demonstrated, to periosteum.

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Synthesis of cell penetrating peptides for targeting tumors

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Chemotherapy is one of the most common strategies for managing cancers. However most chemotherapeutics suffered from poor tumor targeting ability and high drug-originated side effects. As a result tumor site-specific drug delivery and penetration are two major challenges faced in chemotherapy. In this context, access to a drug delivery vehicle that could enable a simple and rapid multi-cargo installation, combining a cytotoxic warhead and a tumor adaptable homing element, could amplify the therapeutic potential of current drugs. Various peptide groups have been developed to overcome the penetrating atargeting problems such as CPPs (cell penetrating peptides) and TTPs (tumor targeting peptides). CCPs elevate membrane penetration, cell internalization and are widely used to enhance the intracellular delivery of various cargoes and nanoparticles while TTP peptides such as RGDs and NGRs are specific for tumor-related surface markers, such as membrane receptors, and can be used to deliver cytotoxic cargo (i.e. drugs or a cytotoxic peptide) specifically to tumor tissue or vasculature. Those two type of peptides can be combined and conjugated with a specific drug so as to improve cellular uptake and antiproliferative effect in specific cancer cells.

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The use of analytical techniques in drug design

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The rational drug design is a rapidly developing field with a number of successes being recorded during the last decades. Before the 1980s it was impossible to rationally design and develop new drugs. However, the revolution in the proteomics and structural genomics, the completion of the human genome project as well as the developments in information technology provided new views in the way novel drugs are designed. Today, two approaches are widely used in the drug design process; the first approach called the ligand-based drug design is used when the structure of the drug-target is unknown. The second approach known as the structure-based drug design method is widely used by the structural biologists to design new drugs in case the structure of the drug-target is already known. This second approach is part of the most drug discovery projects.

Concerning the drug-targets, the majority of the known ones are proteins. In order to use the structure-based approach for protein drug-targets, their structure should be firstly determined. The two main techniques that are used for this purpose are the X-ray Crystallography and Nuclear Magnetic Resonance (NMR) Spectroscopy. The technique of X-ray Crystallography is quite simple, the determination of the structure is easy if the protein is crystallized, while the structure of proteins with a high molecular mass could be determined. However, the requirement of the crystallization of the protein is the major limitation of X-ray Crystallography. For those proteins that are difficult to be crystallized NMR Spectroscopy in solution can be applied. Furthermore, NMR Spectroscopy could be used for the study of the protein dynamic properties, as well as for the investigation and detection of the binding interactions between the protein-target and candidate ligands. The low molecular mass of the proteins (35-50kDa) that can be studied via NMR Spectroscopy till today is the main drawback of the analytical technique. Consequently, these two techniques are usually used complementary in the process of drug design and discovery.

Finally, the development of cryo-electronic microscopy could bring new opportunities in the field of structure biology and assist in the drug design process as it combines the advantages of the two aforementioned techniques and no crystallization of the protein is required. With the development of the technology of cryo-electronic microscopes the limitations of the method could be overcome. In conclusion, these three analytical techniques could function complementary in order to design new and innovative pharmaceutical molecules.

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Exploring the gut-thyroid axis in paediatric coeliac disease patients of Hellenic origin - a novel immunogenetics strategy

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Objectives and study: Differential diagnosis and theranostics of a series of autoimmune inflammatory disorders remain challenging as we still need to dissect the molecular determinants and cross-talk in the cell signaling of the gut-thyroid axis. Several genetic, epidemiological, clinical, serological, and pathophysiological data indicate that coeliac disease is associated with autoimmune thyroid disorders and in particular, Graves' disease. Today, no clear nomogram is effective to allow for optimum disease management and patient stratification. Herein, we explore the role of selected genomic variants for overlapping susceptibility between Graves' disease and paediatric coeliac disease aiming for an immunogenetic model towards the identification of coeliac disease patients with an increased risk of developing Graves' disease.

Methods: Extensive data mining, pathway analysis and literature review resulted in the selection of *CTLA4, BACH2* and *IL23R* variants. For data validation, coeliac paediatric patients of Hellenic origin (n=109) and their ethnically matched counterparts (n=111) were genotyped by PCR and Sanger sequencing. Hardy-Weinberg equilibrium was determined by Pearson's goodness-of-fit chi-square, log-likelihood ratio chi-square and Exact tests. Genotype and allele frequencies were evaluated by the Fisher's Exact test. A two-tailed p-value of <0.05 was considered statistically significant. The R project for statistical computing (R i386 3.2.1) was used.

Results: Selected *CTLA4, BACH2* and *IL23R* variants may account for the overlapping susceptibility between Graves' disease and

paediatric coeliac disease in patients of Hellenic origin.

Conclusion: *CTLA4, BACH2* and *IL23R* variants may serve as the building block of a nomogram to optimize Graves' and Coeliac disease management and patient stratification.

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Use of a novel Graphite/SiO_2 hybrid electrode modified with hybrid organic-inorganic perovskites for the determination of losartan

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Keywords: Graphite/SiO 2 electrode, cyclic voltammetry, drug sensor, hybrid organicinorganic semiconductor, exciton

Hybrid organic-inorganic semiconductors (HOIS) have lately been reported for their exceptional optoelectronics properties that place them as ideal candidates for use in the field of light emitting diodes and photovoltaics. However, in the present work for the second time, HOIS are used as the active material of low cost, simple electrochemical sensors [1-3]. HOIS are used as adsorbed modifiers of aGraphite/SiO_2 hybrid electrode (GSiHE) film in order to develop here a simple and efficient method for the sensitive, relatively specific, determination of a strong antihypertensive drug, losartan (LOS). The electrochemical behavior of GSiHE film modified with 3Dperovskites was examined by cyclic voltammetry while its morphology, structural and spectroscopic properties were investigated by field emission scanning electron microscopy, X-ray diffraction, porosimetry, optical and luminescence spectroscopy. Under optimized conditions the modified film electrode demonstrated excellent electrocatalytic activity towards oxidation of LOS in the linear response range for concentrations from 4x10 -5 M to 3.2x10 -4 M (correlation coefficient 0.989) with the limit of detection computed at 3x10 -6 M. The sensor takes advantage of the ability of ions to interact with the HOIS lattice on the GSiHE film; this type of sensor has demonstrated good repeatability, reproducibility and stability and was found to be applicable for use in pharmaceutical tablet samples.

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Molecular pathogenesis of multiple sclerosis. The role of transcription factor Ets-2

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Backround: In multiple sclerosis (MS), pathogenic Th cells (mainly Th1 and Th17) recognize myelin antigens and contribute to the damage to the central nervous system. An important unresolved issue of MS pathogenesis is at which stage of Th cell differentiation errors occur, at the molecular level, that result in the development of autoreactive Th-cells. We previously showed that in healthy individuals the IL-2 gene is repressed in naive Th cells by the transcription factor Ets-2, that binds to ARRE-2 element (distal NFAT binding site) of the proximal IL-2 promoter, pointing to Ets-2 as a crucial factor influencing early events of Th cell differentiation. Importantly, we also demonstrated that Ets-2 suppresses the expression of other genes with Ets-2 binding sites, including cytokines and HIV-1.

Methods: Ten patients with remitting-relapsing MS and 10 age/sex-matched healthy controls participated in the study. Peripheral blood mononuclear cells (PBMCs) were isolated from patients and controls. T helper (Th) cells cells were isolated from PBMCs; Th cells were depleted from activated effector and regulatory Th cells. From the remaining Th cells, naive (CD3+CD4+CD45RA+CD25-HLA-DR-) and memory (CD3+CD4+CD45RO+ CD25-HLA-DR-) effector Th cells were isolated and subjected to various cellular and molecular immunology assays to study Ets-2 expression, function, in vivo binding to ARRE-2 and its effect on cytokine gene expression. Ets-2 gene expression levels were also assayed in in vitro polarized Th cells isolated from lymph nodes and spleens of naive C57BL/6 mice. In addition, Ets-2 relative mRNA expression was assayed in Th cells from wild-type C57BL/6 mice susceptible to experimental autoimmune encephalomyelitis (EAE) and from EAE-resistant Spp-1-/- C57BL/6 mice.

Results: Our results from the MS patients and the controls, showed significantly reduced mRNA and protein synthesis of Ets-2 in naive Th cells from MS patients, lack of Ets-2 binding to the ARRE-2 of the IL-2 promoter in vitro and in vivo, and significantly higher constitutive expression levels of cytokines in the patients' Th effector cells (IL-2, IL-17 in naive Th cells and TNF-α, IFN-γ in memory Th cells). Our results from mice showed that Ets-2 is differentially expressed in Th subsets, non-differentiated Th (control), and T regulatory cells. Non-differentiated control Th cells had the highest Ets-2 relative expression. In addition, Th cells isolated from draining lymph nodes of EAE-resistant mice showed a 3-fold elevated expression of Ets-2 compared with EAE-susceptible mice. Conclusions: We suggest that in MS patients low-level synthesis and dysfunction of Ets-2 in Th cells are responsible for downstream aberrant Th cell differentiation resulting in the creation of pathological Th1 andTh17cells [1-2].

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Neuronal sorting and degradation of Tau protein in Stress and Alzheimer's disease brain pathologies

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Despite emerging studies implicating Tau in neuronal atrophy and cognitive impairment associated with Alzheimer's disease (AD), the physiopathology of the disorder is complex and poorly understood. Chronic environmental stress and the major stress hormones, glucocorticoids (GC), are suggested precipitating factors for AD, and have been shown to trigger Tau hyperphosphorylation, accumulation and downstream Tau-dependent neuronal atrophy and malfunction. However, the mechanisms that regulate Tau clearance and degradation remain unclear. In the current studies, we use in vitro and in vivo studies to uncover the role of endolysosomal and autophagic pathways in Tau proteostasis under control and pathological conditions providing novel intracellular, molecular, neurostructural and behavioral analysis. We demonstrate for the first time that Tau undergoes degradation via endolysosomal sorting in a pathway requiring the small GTPase Rab35 and the endosomal sorting complex required for transport (ESCRT) machinery [1]. Interestingly, we detect a phospho-dependent selectivity of Tau sorting into the Rab35/ESCRT pathway.

Furthermore, we find that high GC levels impair Tau degradation by suppressing Rab35 expression and ESCRT machinery which leads to accumulation of Tau. Importantly, Rab35 gain-of-function rescues GC-induced Tau accumulation and related neurostructural deficits both in vitro and in vivo [1]. In addition, stress and high GC trigger an mTOR-dependent inhibition of autophagy, leading to accumulation of Tau aggregates and cell death in AD Tg mouse and cell models [2]. In parallel, we found that environmental stress and GC disturb cellular homeostasis and trigger insoluble accumulation of different RNA-Binding Proteins forming Stress granules (SGs). Interestingly, an mTOR-driven pharmacological stimulation of autophagy attenuates the GC-driven accumulation of Tau and SG-related proteins as well as the related cell death, suggesting a critical interface between autophagy and the SG-related proteins response in the neurodegenerative role of chronic stress. Conclusively, these studies indicate that the Rab35/ESCRT pathway and autophagy are essential for Tau clearance and part of the mechanism through which chronic stress precipitates AD. Tau accumulation and related neuropathology is associated with multiple neuropathological conditions, including Alzheimer's disease, frontotemporal dementia, and chronic stress. Therefore, identifying the cellular pathways responsible for Tau intra- and extra-cellular trafficking, as well as positive and negative regulators of these pathways, has broad therapeutic relevance.

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Antigen presentation by tolerogenic dendritic cells: the MOG35-55 -mannan conjugate paradigm. A potential therapeutic vaccine for Multiple Sclerosis

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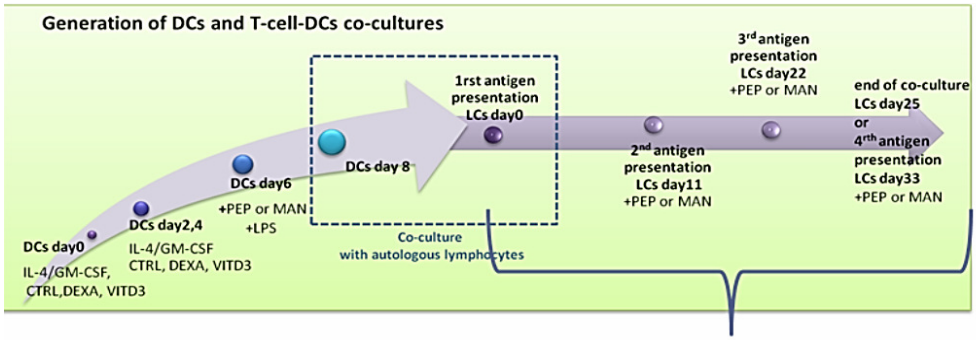
Multiple sclerosis (MS) is an autoimmune disease,which affects the central nervous system. The pathogenic mechanism of MS is orchestrated mainly by autoreactive T and B cells, that escaped the mechanisms of central and peripheral immunological tolerance. The induction of immunological tolerance through the action of dendritic cells is a new-introduced strategy for the treatment of MS. The aim of this study is the generation and the study of antigen presentation of the mannan-conjugated peptide MOG35-55 by tolerogenic dendritic cells (tolDCs), which present the peptide to T cells in order to induce tolerance. To this end, peripheral blood mononuclear cells (PBMCs) were isolated from patients with relapsing-remitting (RR-MS) and age- and sex-matched healthy individuals (controls). PBMCs were differentiated in several types of DCs in the presence of IL-4 and GM-CSF, with or without the addition of dexamethasone (DEXA), vitamin D3 (VitD3) or the combination DEXA+VitD3. At the end their differentiation, DCs were loaded with the MOG 35-55 -mannan conjugate or mannan only, and received the lipopolysaccharide (LPS) maturation signal. They were subsequently co-cultured with autologous PBMCs in the presence of IL-2 for 3 or 4 antigen-presentation circles (Figure 1). The phenotypes of DCs and T cell populations were analyzed using flow cytometry. The cytokine secretion profiles of DCs and T cells were determined by the Cytometric Bead Array method for the cytokines IL-1β/IL-2/IL-4/IL-6/IL-8/IL-10/IL-12p70/IL-17A/TNF-α/IFN-γ and ELISA for TGF-β1. The study and analysis of DCs on day 8 revealed that tolDCs had lower surface expression of CD80 and CD86 molecules and higher IL-10 secretion levels than mature DCs, and this allowed the phenotypic and functional separation between mature and tolerogenic DCs. The co-cultures of PBMCs with the different types of DCs, after 3 or 4 antigen presentation cycles, promoted the generation of memory of CD4 but not of CD8 T cells. From the estimation of activation levels of CD4 T cells, we observed an inhibition of activation in the co-cultures with tolDCs, which presented the MOG 35-55 -mannan conjugate. These results were followed by simultaneous increase in the percentages of exhausted CD4 + PD-1 + and regulatory CD4+CD25 high FoxP3 + T cells and the secretion of IL-10 or/and TGF-β1 (Figure 1). Our

results suggest that tolDCs loaded with the MOG 35-55 -mannan conjugate, which we generated in vitro, induce T cell tolerance and can be used as a therapeutic vaccine for MS.



T cells immune response		
	1η antigen presentation	4η antigen presentation
CTRL-DCs +PEP	Th1 (IL-6, TNF-α, IFN-γ)	Th1 (IL-6, TNF-α, IFN-γ) Reduced numbers of Tregs
DEXA-DCs +PEP	Tr1 (IL-10), Th1 (IL-6, IFN-γ /Th2 (IL-4)	Tr1 (IL-10, TGF-β1) Stable numbers of Tregs
VITD3-DCs +PEP	Tr1 (TGF-β1+ ↓IL-6)	Tr1 (IL-10) ↑Tregs
VD-DCs +PEP	Th2 (IL-4)	

Figure 1. T cell responses to co-culture with DCs presenting the MOG35-55 antigen. Upper panel: Time line of dendritic cell (DC) generation and antigen presentation to T cells. Lower panel: T cell responses to MOG35-55 presented by different DC populations

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The Origin of the Chemical Elements

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Everything we see in the Universe — galaxies, stars, nebulae, planets and humans — is comprised of atoms of the 92 chemical elements found free in Nature. Hydrogen and most of the helium were born in the first minutes of the universe 13.8 billion years ago. For each 16 particles formed at that time, 4 fused together to form a helium nucleus, in other words 25% of the protons became helium and 75 % were hydrogen. At the same time in other parallel reactions, we had the creation of small quantities of helium 3, beryllium 7, and lithium 7. Further creation of any other chemical elements was delayed until the creation of the stars (hundreds of millions of years later and up to the present.

In the thermonuclear core of the stars hydrogen is converted by fusion into heavier elements up to iron. The remaining elements are created in supernova explosions. This spectacular end of a giant star's life results in the creation of a black hole or a neutron star (pulsar) that spins dozens or even hundreds of times every second. The collision of two such neutron stars leads to the creation of gravitational waves and a Black Hole with 90% of the two pulsars' materials. These results in the creation of heavy chemical elements in the amount of 16,000 times the Earth's mass, including gold in an amount equal to 800 times the Moon's mass.

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Therapeutic approaches in multiple sclerosis mouse models using mannan-conjugated peptides

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Myelin peptides conjugated to oxidized mannan (OM) protected mice against the experimental animal model of multiple sclerosis Experimental Autoimmune Encephalomyelitis (EAE) in prophylactic and therapeutic protocols. Protection was peptide-specific and associated with reduced antigen-specific T cell proliferation. OM-MOG induced active T cell tolerance; because passive transfer of OM-MOG loaded DC suppressed ongoing EAE.

Our results show that mannan-conjugated myelin peptides protect mice against EAE through the expansion of antigen-specific Th1 and Th17 cells with impaired proliferative responses and APC-induced co-stimulatory signals that are required for licensing them to become fully pathogenic T cells. This approach can be a promising tolerance inducing therapeutic strategy for the treatment of Multiple Sclerosis.

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Search for infectious agents contributing in Breast Cancer and Hodgkin's Lymphoma

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Epidemiological data indicate a potential relation between the consumption of bovine meat and dairy products and the incidence of breast and colon cancer. Specifically, the consumption of milk and dairy products originating from specific cattle species seems to play a significant role in the development of breast cancer. Our group has recently isolated a number of novel circular single-stranded DNAs (Bovine Milk and Meat Factors, BMMFs) from bovine sera of healthy cattle and commercially available dairy products, as well as from brain and serum samples of patients suffering from Multiple Sclerosis (MS). This project aims at the identification of such episomal DNA agents in breast cancer. Therefore, total DNA is extracted from breast cancer tissue samples as well as normal adjacent to tumor controls. Subsequently, the DNA is subjected to Rolling Circle Amplification (RCA) using random primers in order to specifically amplify circular DNA molecules, which are then identified by Next Generation Sequencing and de novo assembly. In addition, our efforts are focusing on the search for a permissive system for the identified BMMFs. Replication competence of the MS brain isolate MSBI1.176 was shown in two Hodgkin's Lymphoma cell lines, the L-1236 and L-428 establishing a long-term persistence in human cells. Positive results from this study would provide useful information about potential risk factors of bovine origin contributing to the pathogenesis of breast cancer and Hodgkin's Lymphoma, which would allow for novel therapeutic strategies for fighting these diseases.

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Defining the "actionable genome" toward risk assessment for recurrent cardiovascular events

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Objectives and study: Cardiovascular disease remains a leading cause of death and at the same time, a global public health issue of major socio-economic impact. Optimal patient stratification and decision-making in the clinic demand the in-depth understanding of the (patho)physiology of the cardiovascular system, not only for a cardiovascular event to be successfully dealt with, but also to assess the risk of its recurrence. Herein, we aim to perform a state-of-the-art strategy towards risk assessment and better-informed patient stratification via multi-omics data integration.
Methods: Following the recruitment of patients with a cardiovascular event (first or a recurrent one) of Hellenic origin, we performed text- and data- mining and used a series of databases and chemoinformatics to explore a panel of genomic variants and their association to cardiovascular events and their recurrence. Such datasets are integrated to miRNAs and proteomics/metabolomics datasets to reveal the so-called “actionable genome” and map inter-individual variability
Results: Our preliminary datasets indicate that selected *NOS3, NOA1, PHACTR1, PCSK9, APOB, MRAS, GUCY1A3, CDKN2B-AS1, BCAS3, VEGF* and *SMARCA4* variants may account for the cardiovascular events in question and their recurrence.
Conclusion: Such a multi-omics strategy may serve as the building block of a nomogram to optimize cardiovascular disease management and patient stratification with an emphasis on risk assessment.

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A theragnostic device with photo regulated drug dosing and cancer microenvironment sensing character

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Gemcitabine (dFdC) is an antimetabolite, a nucleoside analogue and is widely used as an anticancer agent against several solid tumors. Although its potency, it has two main therapeutic limitations: it lacks cancer cell selectivity and is rapidly transformed to an inactive uridine (dFdU) metabolite leading to low bioavailability and poor stability. To surmount these drawbacks, we constructed a theranostic molecular device that is able to sense and kill cancer cells integrating both photo regulated drug dosing properties and cancer microenvironment sensing characteristics.

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REVIEW CLINICAL PHARMACOLOGY AND
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Acoustic Ring Biosensor

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Introduction:Manipulation of elastic or acoustic waves is of fundamental importance in the research area of wave propagation in nature [1]. Taking advantage of elastic or acoustic waves is a challenge which could provide great opportunities evolving technological applications in almost all range of phononic spectrum [2]. In the field of Acoustic Resonators one of the most interesting phenomena is the well-known Whispering Gallery Modes (WGMs). Lord Rayleigh investigated the acoustic waves clinging to the dome of St. Paul's Cathedral in London [3][4].

Computational method: In this computational work, we use the Finite Difference Time Domain (FTDT) method to numerically study the acoustic resonances in a ring resonator [5]. The suggested ring has inner radius (R_{in}) 25 grid points, outer radius (R_{out}) 30 grid points and its thickness is 8 grid points (as shown in **Figure 1)**. The possibility of performing sensor applications with this device was examined. The ring is immersed into different liquids and the resonances of the ring were calculated for each liquid. The sensitivities of the ring were calculated by the sensitivity parameter of the sensor that is defined as the ratio of the difference between the f_1 (the frequency resonance for the first liquid that the ring was immersed) and f_2 (the frequency resonance of the second liquid) to f_2.

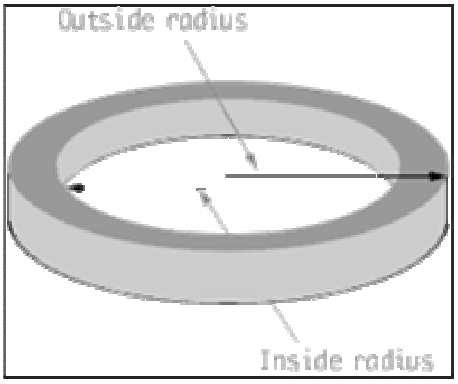

Figure 1. The geometric parameters of the ring sensor structure where R_{out} and R_{in} are the outer and inner radius of the ring.

Results: According to the different resonant frequencies of the disk when immersed into different liquids sensing application could appear due to those differences. The sensitivities of the ring were calculated, and the results showed strong evidence that the proposed device could be a very promising candidate for sensing applications. **Table 1** presents the results of the sensitivity parameters when ring is consisted by aluminum and it is immersed into 100% propanol and water. It is important to be mentioned here that several different materials where examined both for the ring and the liquid.

Table 1. Sensitivity parameters for the three wave propagation directions

Direction	Sensitivity
u_x	0.041
u_y	0.069
u_z	0.081

Our study includes, also, the case where the disk is placed above a substrate and the results show that the sensing performance of the disk is not affected by the presence of the substrate. When the liquid is blood or any other biological liquid then the device could be considered as a biosensor with very promising potential applications.

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Design and Pilot Manufacturing of electrochemical biosensor for the detection of organic halogen compounds in the water

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In the present study we describe the design and the manufacturing of an electrochemical biosensor, which was used for the detection of organohalides in water. Iron (III) protoporphyrin IX chloride (hemin) was physically adsorbed on the surface of nanocrystalline SnO_2 film electrodes on ITO glass or plastic substrates like ITO-PET. The mesoporous structure and the excellent optical and semiconducting properties of this inorganic support allows electrochemical and spectroelectrochemical studies of the immobilized hemin redox function and moreover, provide an attractive approach for the reduction of organohalides in water. In the first part of this study, we present the organohalides used. In particular, chloroform, trichloroacetic acid and carbon tetrabromide presence in groundwater can exert long-term toxic effects, present serious health risks as they have been linked to cancer and cause ozone depletion. Therefore, their analytical detection has been the object of high interest in order to find proper ways to monitor and to quantify their presence. Analytical methods used for their determination in water are mentioned and special emphasis is given to electrochemical techniques and the advantages they offer for the detection of analytes. Common electrodes, modified or not, for the detection of organohalides are also mentioned. In the second part of this work, the biosensor development is presented. The use of mesoporous SnO_2 film electrodes modified with a molecular catalyst, such as hemin allows the determination of organohalides in water through their electrocatalytic reduction, using cyclic voltammetry (CV) and differential pulse voltammetry (DPV). The film electrodes were characterized using scanning electron microscopy (SEM), X-ray diffraction (XRD) and UV-Vis spectroscopy. This study is based on previous work and experimental methods developed in our laboratory.[1-3]

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My recent experience at the Cambridge Immerse Summer Programme: The Challenge of Research in Biosciences

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This talk is about the presenter's experience in the short-term international academic Cambridge Immerse Biology Course; a joint course, co-organised by the Universities of Cambridge and Oxford for high-school or first-year university students. The main objective of the course is to introduce students to university life while approaching the field of Biology from a completely innovative perspective; helping them make a more knowledgeable decision about their future careers in the field of Biosciences. The programme pushes participants to work collaboratively and dives deep into advanced topics not typically covered in a secondary school syllabus. As participants work through the curriculum, they spend their days studying on campus at a Cambridge University college and increasingly assume independent responsibility for their learning. By the end of the course, participants not only have a working understanding of complex first-year Biology concepts, but a new appreciation for the routines and responsibilities of university.

My interest to visit and experience the Cambridge Immerse Summer Programme was mainly triggered after meeting James Watson in the 17th Medicinal Chemistry Conference in Spetses, Greece, August 29-31, 2016 celebrating the 50th Anniversary of his first visit in the island in 1966 with Francis Crick with whom they discovered the DNA Double Helix. [1,2]

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From Angiotensin to Sartans: A New Generation of anti-hypertensive drugs and their perspectives

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The blockade of the renin-angiotensin system has been recognized as being of primary importance in the treatment of hypertension and congestive heart failure. A breakthrough came with the discovery and development of angiotensin converting enzyme (ACE) inhibitors that suppress the metabolism of the decapeptide angiotensin I to angiotensin II (ANG II). Taking antihypertensive therapy a stage further was realized through the development of ANG II receptor antagonists. Since late 1970s, a large number of ANG II linear and cyclic peptide analogues have been synthesized in order to develop a potent ANG II receptor antagonist. Structure-activity relationship studies have identified the pharmacophores of the molecule and several conformational models for ANG II have been proposed. The suggested by G. Moore & J. Matsoukas Charge Relay System-Ring Cluster Conformation of ANG II, which is based on NMR and chemical reactivity studies, looks closer to the actual ANG II conformation (1,2,3,4). A new generation of angiotensin antagonists or angiotensin mimetics or ARBs (Angiotensin Receptor Blockers) was set to replace the angiotensin converting enzyme inhibitors for the treatment of cardiovascular diseases (2). The development of drugs that selectively block angiotensin receptors has resulted largely from a process of trial-and-error medicinal chemistry on an early lead. Since the disclosure of weakly active non-peptide ANG II receptor antagonists in 1982 much effort has been expended on the development of potent analogues in this series of compounds. This work culminated in the synthesis of the first ARB, Losartan, a highly potent orally active angiotensin II receptor antagonist. Series of mimetics have been prepared in an attempt to gain a better understanding of the mode of action of this type of non-peptide ANG II receptor antagonist. As a result of this effort, a number of effective ARB drugs has been developed and commercialized with approved indications not only for hypertension, but also for other cardiovascular diseases.

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Ομιλία Δημάρχου Ήλιδας

Χρήστος Χριστοδουλόπουλος
22 Σεπτεμβρίου, 2018

«Εξοχότατε Κύριε Πρόεδρε της Δημοκρατίας,

Σεβασμιότατε,

Κυρίες και Κύριοι,

Η Ήλιδα, η γενέτειρα των Ολυμπιακών Αγώνων, σας καλωσορίζει στον Πολυχώρο Πολιτιστικών Δραστηριοτήτων, όπου οι Αξίες που μας οδήγησαν και μας οδηγούν στο πέρασμα των αιώνων, βρίσκουν τη σύγχρονη στέγη τους. Η Παιδεία που αλλάζει τον κόσμο, είναι αυτή που μετασχηματίζεται σε βίωμα και έργο, που παραδειγματίζουν θετικά και κινητοποιούν τους Πολίτες προς την κατεύθυνση της ατομικής και συλλογικής βελτίωσης. Ο Πολιτισμός, ως συστατικό στοιχείο, αλλά και λαμπρό αποτέλεσμα της Παιδείας, για να προσλάβει τη μέγιστη αξία του, δεν αρκεί να περνά και να εντυπωσιάζει στιγμιαία, όπως συμβαίνει με πλείστες όσες καλλιτεχνικές εκδηλώσεις φιλοξενούνται κάθε χρόνο, τόσο στον Δήμο μας, όσο και στους υπόλοιπους Δήμους της Χώρας. Ο Πολιτισμός πρέπει να φωλιάζει στην καθημερινότητα των Πολιτών και των συλλογικοτήτων της κοινωνίας και να προσφέρεται απλόχερα σε όλους όσους το επιθυμούν να είναι κοινωνοί του. Οι καλλιτέχνες, οι ανήσυχοι του κόσμου, πρέπει να έχουν τόπο να τον αγαπούν και να τους αγαπά. Αυτό ακριβώς, είναι ο Πολυχώρος που εγκαινιάζουμε απόψε. Ένας τόπος για τους ανήσυχους. Ένα σπίτι για την δημιουργία. Ένας κόμβος ανοιχτής πολιτισμικής επικοινωνίας. Ένα σπίτι για τις ψυχές που απελευθερώνονται μέσα από την τέχνη και μας προσκαλούν σε ένα ταξίδι πέρα από τον στενό ορίζοντα της καθημερινότητας. Για πολλά χρόνια, εδώ που στεκόμαστε σήμερα, λειτουργούσαν φυλακές. Ήταν καιροί με λίγα σχολεία και μεγάλη ανέχεια. Σήμερα, παρά το γεγονός πως έχουμε πολλά σχολειά και ασύγκριτα μεγαλύτερη ευημερία σε σχέση με εκείνα τα χρόνια, χτίζουμε νέες φυλακές. Άρα κάτι κάνουμε λάθος. Αυτό το λάθος είναι πως δεν εμβαθύνουμε στην Παιδεία, αλλά αντιλαμβανόμαστε το προϊόν της γνώσης και το καταναλώνουμε. Αυτό το λάθος είναι, πως έχουμε αφεθεί σε έναν παθητικό ρόλο, σε ένα ρόλο θεατή της Παιδείας και του Πολιτισμού και αντιλαμβανόμαστε μόνο λίγες στιγμές τους, από ένα κάθισμα θεάτρου ή από τον υπολογιστή και την τηλεόραση. Η νέα, παγκόσμια φυλακή που χτίζουμε, εξαγοράζοντας ησυχία, είναι η κοινωνία της αντίληψης και του λειτουργικού αναλφαβητισμού. Η εσωστρέφεια. Η συρρίκνωση της δημιουργίας. Η απαξίωση του ταλέντου και η αποθέωση της γενίκευσης.

Κυρίες και κύριοι,

Ο Πολυχώρος αυτός, πρέπει να γίνει, στα χέρια των δημιουργικών Πολιτών, το τούνελ απ'όπου θα δραπετεύσουμε από έναν στείρο και ανέπνευστο κόσμο. Ο Πολυχώρος αυτός, ξαναδίνει στην Ήλιδα και σε όλη την Ηλεία, ένα σημείο συνύπαρξης των ανήσυχων πνευμάτων και ταλέντων, που μπορούν να γίνουν εφαλτήριο για μια νέα, ευοίωνη πραγματικότητα. Στην Ηλεία και στην Ήλιδα, οι οποίες, για περισσότερα από εκατό χρόνια, βιώνουν μια ανιστόρητη διάσπαση. Ο ξένος παράγοντας, εκμεταλλευόμενος και την Ελληνική αδιαφορία, απέσπασε το Ιερό της Ολυμπίας και το μετέτρεψε, σταδιακά, σε έναν ακόμα τουριστικό προορισμό. Το «όλον» του Ολυμπιακού Χώρου κατατμήθηκε και το μείζον μέρος του αρχαίου Ολυμπιακού περιβάλλοντος, παραμένει στην αφάνεια. Η αρχαία Ήλιδα, η γενέθλια Πόλη των Αγώνων και των Αξιών τους, ο Ιερός τόπος προετοιμασίας αθλητών και Ελλανοδικών, η αφετηρία της ΟΛΥΜΠΙΑΚΗΣ ΠΟΜΠΗΣ, παραμένει κάτω από την επιφάνεια της γης και αποστερεί από το Εθνικό πολιτιστικό απόθεμα, τον ΕΝΙΑΙΟ ΟΛΥΜΠΙΑΚΟ ΧΩΡΟ. Έναν πολιτισμικό κόμβο Οικουμενικής εμβέλειας.

Εξοχότατε Κύριε Πρόεδρε,

Νομίζω πως οι συνθήκες ωρίμασαν, ώστε η Πολιτεία να πράξει το χρέος της και να επανενώσει τον Ολυμπιακό Πολιτισμό, δίνοντας

το παράδειγμα της Οικουμενικής επανένωσης του Ελληνισμού μέσα από τον πολιτισμό. Δίνοντας το παράδειγμα μετάβασης από την αναλώσιμη τουριστική αντίληψη, στην Παιδευτικής πολιτισμική γνώση. Αυτό εγκαινιάζουμε απόψε. Αυτό γιορτάζουμε απόψε. Την ευκαιρία να απελευθερωθούμε από τα δεσμά της απλής αντίληψης. Την δυνατότητα να συνδυάσουμε την γνώση του επιστητού, την επιστήμη, που εκπροσωπείται από τους εξέχοντες επιστήμες που συμμετέχουν στο Διεθνές Συνέδριο Ιατρικής Χημείας, με την δύναμη της μουσικής, της ποίησης, και της θαυμαστής γλυπτικής του Στάθη Λεοντή. Για να δραπετεύσουμε από την παθητικότητα και να απελευθερώσουμε ένα υπαρκτό και, δια του παραδείγματος, αυξανόμενο, Κίνημα Πολιτισμού και Γνώσης, ικανού να εκπέμψει μηνύματα αντάξια της ιστορίας μας. Αλληλεπίδραση και ζύμωση όλων των στοιχείων της Παιδείας. Αυτή είναι η απάντηση στους καιρούς της κρίσης. Ο Πολυχώρος αυτός, όμως, δεν ήρθε από το πουθενά. **Για να πάρει σάρκα και οστά, εργάστηκαν και συνεργάστηκαν πολλοί. Στο σημείο αυτό, θέλω να συγχαρώ τον πρώην Δήμαρχο Ήλιδας Γιάννη Λυμπέρη, γιατί, επί της θητείας του, μελετήθηκε, ξεκίνησε και μορφοποιήθηκε αυτή η εξέχουσα υποδομή.** Φυσικά και πριν ο Δήμος μας ευτύχισε να έχει δημάρχους που με τις υποδομές πολιτισμούς και τους θεσμούς που δημιούργησαν συνέβαλαν στο να αποτελεί διαχρονικά η περιοχή μας τον πολιτιστικό ηγέτη του Νομού. Θέλω, επίσης, να ευχαριστήσω όλους τους πολιτικούς και υπηρεσιακούς παράγοντες, που συνέβαλαν στην ωρίμανση, την χρηματοδότηση και υλοποίηση του έργου. Τέλος, ένας έπαινος αξίζει και στην δική μας Δημοτική Αρχή, γιατί ξεπέρασε τα σύνθετα προβλήματα που υπήρχαν, ολοκλήρωσε το έργο, το κατέστησε λειτουργικό και το παραδίδει σήμερα στο λαό της Ήλιδας. Με αυτόν τον συμβολισμό, θα ήθελα, να κλείσω και τον χαιρετισμό μου. Ότι, για να δραπετεύσουμε από την εσωστρέφεια της μικροπολιτικής που μικραίνει τους τόπους, χρειαζόμαστε μεγάλες συνέργειες και αποτελεσματικές συνέχειες, με ενότητα και πολιτισμό, σε όλα τα επίπεδα. Αξιότιμοι Καθηγητές του Πανεπιστημίου Πατρών και εκπρόσωποι της Διεθνούς Ακαδημαϊκής Κοινότητας, Καθηγητή Ιωάννη Ματσούκα, Αξιότιμε καθηγητά και κάτοχε του Νόμπελ Ιατρικής κύριε Τσουρ Χάουζεν, Αγαπητή και εξέχουσα επιστήμονα, μα πρώτα απ' όλα συμπολίτισσα κυρία Αποστολοπούλου, Αγαπητοί εκπρόσωποι του πολιτικού και καλλιτεχνικού κόσμου, Φίλες και φίλοι συμπολίτες της Ήλιδας, Ιδιαιτέρως κλείνοντας θα ήθελα για μια ακόμη φορά να ευχαρίστησαν την αυτού εξοχότητα, τον πρόεδρο της Ελληνικής Δημοκρατίας κ. Προκόπιο Παυλόπουλο για την τιμή που μας έκανε να προσδώσει με το προσωπικό και το θεσμικό του κύρος τη μέγιστη δυναμική σε αυτόν τον υπέροχο χώρο. Σας ευχαριστώ!»