Ελληνική Εταιρεία Βασικής & Κλινικής Φαρμακολογίας

ΕΕΒΚΦ

10ο ΠΑΝΕΛΛΗΝΙΟ Συνέδριο

Ελληνικής Εταιρείας Βασικής και Κλινικής **ΦΑΡΜΑΚΟΛΟΓΙΑΣ**

25-27 ΜΑΪΟΥ 2018

Ξενοδοχείο **GRAND SERAI , Ιωάννινα**

τελικό πρόγραμμα

“Για εμάς η ποιότητα στην παραγωγή σημαίνει πραγματική φροντίδα για τον άνθρωπο.”

Στα 90 χρόνια λειτουργίας της ΒΙΑΝΕΞ στο κέντρο της φιλοσοφίας μας υπήρξε πάντα η ποιότητα στην παραγωγή. Με πάνω από 1.000 εργαζομένους, στα 4 υψηλών προδιαγραφών εργοστάσια του ομίλου παράγουμε – για τον εαυτό μας ή για λογαριασμό τρίτων – φαρμακευτικά προϊόντα σύμφωνα με τις πιο αυστηρές διεθνείς απαιτήσεις. Μέσα από διαρκείς έρευνες και μελέτες του υψηλής εκπαίδευσης προσωπικού μας και των 440 και πλέον επιστημονικών συνεργατών μας καθιερωθήκαμε στην κορυφή των πιο αξιόπιστων φαρμακευτικών εταιριών στην Ελλάδα και διεθνώς.

Με βάση την αδιαπραγμάτευτη ποιότητα των προϊόντων μας καταφέραμε να δημιουργήσουμε μια μόνιμη σχέση εμπιστοσύνης με τον Ιατρικό και Φαρμακευτικό κόσμο, διανέμοντας τα προϊόντα μας και καλύπτοντας το 100% των νοσοκομείων της Ελλάδας, των φαρμακεμπόρων και των συνεταιρισμών φαρμακοποιών.

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Ελληνική Εταιρεία Βασικής & Κλινικής Φαρμακολογίας

ΕΕΒΚΦ

ΠΕΡΙΕΧΟΜΕΝΑ

Χαιρετισμός Προέδρου

Εκ μέρους της Οργανωτικής Επιτροπής του 10ου Πανελλήνιου Συνεδρίου Βασικής και Κλινικής Φαρμακολογίας, έχω την ιδιαίτερη τιμή και χαρά να σας προσκαλέσω στην πόλη των Ιωαννίνων από τις 25 έως τις 27 Μαΐου 2018.

Σας καλούμε, να πλαισιώσετε τις εργασίες του Συνεδρίου και να παρουσιάσετε τις ερευνητικές σας εργασίες σε θέματα καθημερινής ορθής πρακτικής και επερχόμενης καινοτομίας στον τομέα του φαρμάκου.

Το συνέδριο αποτελεί την κορυφαία εκδήλωση της εταιρείας μας, μία εκδήλωση θεσμό και ελπίζουμε ότι όλοι θα συμμετέχετε ενεργά με σκοπό την ενημέρωση και την ανταλλαγή απόψεων σε καίρια ζητήματα που αφορούν την φαρμακολογία σε επίπεδο έρευνας και εκπαίδευσης, τους μελλοντικούς στόχους της φαρμακοβιομηχανίας και τον ρόλο του φαρμακολόγου σε αυτό το πλαίσιο.

Είναι ευκαιρία να συναντήσετε κορυφαίους φαρμακολόγους με παγκόσμια ακτινοβολία, που θα αναπτύξουν θέματα αιχμής στην έρευνα και καινοτομία γύρω από το φάρμακο. Να διερευνήσετε πιθανές συνεργασίες και να ανταλλάξετε πληροφορίες με νέους αλλά και έμπειρους ερευνητές, που δραστηριοποιούνται στον τομέα της Φαρμακολογίας.

Με τιμή,

Η Πρόεδρος της Οργανωτικής Επιτροπής

Μαρία Κωνσταντή
Καθηγήτρια, Διευθύντρια του Εργαστηρίου Φαρμακολογίας
Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων

ΟΡΓΑΝΩΣΗ

Ελληνική Εταιρεία Βασικής και Κλινικής Φαρμακολογίας
Πρόεδρος: Καθηγητής **Ε. Μανωλόπουλος**

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Διευθύντρια: Καθηγήτρια **Μ. Κωνσταντή**

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	Γ. Λεονταρίτης
	Π. Παππάς

Διοικητικό Συμβούλιο Ε.Ε.Β.Κ.Φ

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Καθηγητής Παθολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων

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Καθηγήτρια Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Κρήτης

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Κούβελας Δημήτριος
Καθηγητής Φαρμακολογίας, Εργαστήριο Κλινικής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

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Τσιάρα Σταυρούλα
Καθηγήτρια Παθολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων

Τσοπάνογλου Νικόλαος
Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Πατρών

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Καθηγήτρια Φαρμακολογίας, Εργαστήριο Φαρμακολογίας, Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

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Χαραλαμπόπουλος Κωνσταντίνος
Καθηγητής Φυσιολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων

Χρήστου Λεωνίδας
Καθηγητής Παθολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων

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Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Κρήτης

Κυπραίος Κυριάκος
Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Πατρών

Μανωλόπουλος Ευάγγελος
Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Δημοκρίτειο Πανεπιστήμιο Θράκης

Παπαπετρόπουλος Ανδρέας
Καθηγητής Φαρμακολογίας, Τομέας Φαρμακευτικής Χημείας, Τμήμα Φαρμακευτικής, Σχολή Επιστημών Υγείας, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

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υποστήριξης του **10ου Πανελλήνιου Συνεδρίου** Ελληνικής Εταιρείας Βασικής και Κλινικής **Φαρμακολογίας**

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Ανδρίκου - Καλέσογλου Κωνσταντίνα
Δημητριάδου Βασιλική
Κουμπατή Αικατερίνη
Κουτσογιάννη Δανάη - Δήμητρα
Παπίλα Μαρίνα
Τζάνη Μαρία
Φίλης Παναγιώτης

ΠΑΡΑΣΚΕΥΗ 25 ΜΑΪΟΥ 2018

09:00 - 10:00	Εγγραφές
10:00 - 11:40	**Στρογγυλό Τραπέζι** ***Ο ρόλος του φαρμακολόγου στην ανάπτυξη και έγκριση νέων Φαρμάκων*** **Προεδρείο: Κ. Αντωνίου, Δ. Κούβελας, Α. Γούλας**
10:00 - 10:20	Ευρωπαϊκός Οργανισμός Φαρμάκου: Ο ρόλος των ερευνητών στη λειτουργία του και η συμβολή του στην ανάπτυξη νέων φαρμάκων **Α. Ταυρίδου**
10:20 - 10:40	Κεντρική διαδικασία για την έγκριση νέων φαρμάκων **Ε. Νικολαΐδη**
10:40 - 11:00	Ο Ρόλος του Φαρμακολόγου **Δ. Κούβελας**
11:00 - 11:20	Προοπτικές ανάπτυξης της ελληνικής φαρμακοβιομηχανίας **Θ. Τρύφων**
11:20 - 11:40	Start up επιχειρήσεις στον τομέα του φαρμάκου **Α. Παπάζογλου**
11:40 - 12:00	*Διάλειμμα Καφέ*
12:00 - 13:30	**Round table** ***Personalized Medicine*** **Chairmen: E. Manolopoulos, G. Karakioulakis**
12:00 - 12:30	Integration of Precision Medicine into Clinical Practice **M. Simmaco,** *Italy*
12:30 - 13:00	VEGF: a novel biomarker for personalised medicine **S. Siest,** *France*
13:00 - 13:30	Pharmacogenomics in the clinic: If not now, when??? **G. Patrinos**
13:30 - 17:30	*Μεσημεριανή Διακοπή*

17:30 - 19:00	**Round table** ***Recent strategies in cancer therapy and novel molecules with anticancer properties*** **Chairmen: P. Pappas, G. Leondaritis**
17:30 - 18:00	Metronomics in Anticancer Therapy **N. Andre,** *France*
18:00 - 18:30	Novel peptides that regulate angiogenesis and cancer cell functions **E. Papadimitriou**
18:30 - 19:00	Chemistry and Biology of Indirubins **L. Skaltsounis**
19:00 - 19:30	*Διάλειμμα Καφέ*
19:30 - 20:00	**Επίσημη Έναρξη - Χαιρετισμοί - Προσφωνήσεις**
20:00 - 20:40	Τιμητική εκδήλωση για τον Ομότιμο Καθηγητή Μάριο Μαρσέλο **Προεδρείο: Ε. Μανωλόπουλος, Μ. Πασχόπουλος** *Παρουσίαση - Εισαγωγή:* **Μ. Κωνσταντή** Τα Φάρμακα στην Αρχαία Ελλάδα - Στάδια Ανάπτυξης της Δυτικής Ιατρικής Σκέψης **Μ. Μαρσέλος**
21:00	***Δεξίωση Υποδοχής/Όρθιο κοκτέιλ***

ΣΑΒΒΑΤΟ 26 ΜΑΪΟΥ 2018

9:15 - 11:00	**Round table** ***New therapeutic approaches in neurodegenerative and neuropsychiatric disorders: Molecular targets*** **Chairmen: A. Papapetropoulos, C. Dalla**
9:15 - 9:45	Neuroanatomy of Stress: Unraveling Neural Circuits in Stress & Anxiety Disorders **E. O. Johnson**
9:45 - 10:15	Tau therapeutics in brain pathology: the link between depression and Alzheimer's disease **I. Sotiropoulos**
10:15 - 11:00	Unmet medical needs in the treatment of depression and clinical development of a differentiated antidepressant **G. Nomikos**
11:00- 11:30	*Διάλειμμα Καφέ*
	Παρουσίαση Αναρτημένων Ανακοινώσεων: Session A **PP1-PP28** *(σελ. 49-76)* *Εκθεσιακός Χώρος*
11:30 - 12:30	**Plenary lecture** **Chairmen: M. Konstandi, E. O. Johnson** Brain-on-a-chip: developing neuroprotective drugs and neuroimplants **A. Gravanis**
12:30 - 13:30	*Γεύμα στο Εστιατόριο Γιασεμί, Grand Serai* *Οι εγγεγραμμένοι συμμετέχοντες παρακαλούνται να επιδεικνύουν την κονκάρδα τους κατά την είσοδο στο χώρο του εστιατορίου*

13:30 - 15:00 Προφορικές Ανακοινώσεις/Oral Presentations SESSION A'

Προεδρείο: Ν. Πιτσίκας, Ε. Παπακωνσταντίνου *(σελ. 27-35)*

OP1

A CRITICAL RE-EVALUATION OF FIRST-GENERATION VANADIUM-BASED PTEN INHIBITORS IN VIVO

G. Aggelis[1], M. Papanikolaou[2], C.E. Andriopoulou[1], B.J Eickholt[3], M. Konstandi[1], T.A. Kabanos[2], G. Leondaritis[1]

[1] Laboratory Of Pharmacology, Medical School, University Of Ioannina, Ioannina, Greece

[2] Section Of Inorganic And Analytical Chemistry, Department Of Chemistry, University Of Ioannina, Ioannina, Greece

[3] Institute Of Biochemistry, Charite-Universitatsmedizin Berlin, Neurocure Cluster Of Excellence, Berlin, Germany

OP2

A NOVEL MODULATOR OF AMPA RECEPTORS AGAINST ALZHEIMER'S DISEASE PATHOLOGY: THE FIRST IN VIVO EVIDENCE

D. Monteiro[1], J. M. Silva[1], S. Ferreira[1], C. Soares-Cunha[1], S. Bretin[2], N. Sousa[1], I. Sotiropoulos[1]

[1] Life And Health Sciences Research Institute (Icvs), School Of Health Sciences, University of Minho, Braga, Portugal, Icvs/3b's–Pt Government Associate Laboratory, Braga/Guimaryes, Portugal

[2] 3pтle Innovation Thırapeutique Neuropsychiatrie, Institut De Recherches Internationales Servier, Suresnes, France

OP3

ALTERED ONE-CARBON PATHWAY BY DIETARY MODIFICATIONS DISRUPTSCARDIAC EXTRACELLULAR MATRIXHOMEOSTASIS AND IMPAIRS NORMAL HEART FUNCTION

A. Strilakou[1], I. Mourouzis[1], A. Lazaris[2], A. Al-Humadi[1], P. Karkakousos[3], C. Pantos[1], C. Liapi[1]

[1] Department of Pharmacology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[2] 1st Department of Pathology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[3] Department of Medical Laboratories, Technological Institute of Athens, Athens, Greece

OP4

MITOCHONDRIA AS PHARMACOLOGICAL TARGETS FOR ANXIETY AND STRESS-RELATED DISORDERS

M.D. Filiou

Department of Biological Applications and Technology, School of Health Sciences, University of Ioannina, Ioannina, Greece

OP5 *(θα παρουσιαστεί ως PP57 , Παρουσίαση Αναρτημένων Ανακοινώσεων: Session A)*
BNN27 EXERTS SIGNIFICANT ANTI-INFLAMMATORY EFFECTS ON T-LYMPHOCYTES DERIVED FROM MICE FOLLOWING CFA-INDUCED INFLAMMATION
S. Poulaki, M. Venihaki
Faculty of Medicine, School of Health Sciences, University of Crete, Heraklion, Greece

OP6
CIRCULATING CELL-FREE DNA IN BREAST CANCER: A VALUABLE TOOL FOR PROGNOSIS AND PREDICTION OF TREATMENT RESPONSE
M. Panagopoulou[1], M. Karaglani[1], I. Balgkouranidou[1], V. Vasilakakis[2], E. Biziota[1], T. Koukaki[1], E. Karamitrousis[1], E. Nena[1], I. Tsamardinos[2], G. Kolios[1], S. Kakolyris[1], E. Chatzaki[3]
[1] Medical School, Democritus University Of Thrace, Alexandroupoli, Greece
[2] Department Of Computer Science & Gnosis Data Analysis, University Of Crete, Voutes, Greece
[3] Medical School, Democritus University Of Thrace, Alexandroupolis Greece & Foundation of Research And Technology Hellas, Voutes, Crete

OP7
EFFECTS OF IMATINIB AND DICHLOROACETATE ACID ON CELLULAR BIOENERGETICS OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS
D. Mavridou, G. Gavriilidis, L. Papadopoulou
Laboratory of Pharmacology, Faculty of Pharmacy, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

OP8
TRIANGULATING BETWEEN DRUG, GENES AND PHARMACOGENOMIC BIOMARKERS TO CLINICALLY IMPLEMENT PRECISION MEDICINE
S. Koutsilieri, G. Patrinos
Faculty of Pharmacy, School of Health Sciences, University of Patras, Patras, Greece

OP9
EFFECT OF EBSELEN ON CENTRAL 5-HT2A RECEPTOR FUNCTION AND EXTRACELLULAR 5-HT IN THE MOUSE
I. Antoniadou[1,2], M. Kouskou[2], T. Arsiwala[2], N. Singh[2], S. Vasudevan[2], G. Churchill[2], T. Sharp[2]
[1] Department of Pharmacy, School of Life Sciences, European University of Cyprus, Cyprus
[2] Department of Pharmacology, University of Oxford, Oxford, UK

15:00 - 17:30	**Round table** ***New therapeutic targets*** **Chairmen: M. Koutsilieris, K. Thermou**
15:00 - 15:30	Serum-derived extracellular vesicles and their potential therapeutic application **M. F. Brizzi,** *Italy*
15:30 - 16:00	Glycosaminoglycans as pharmacological targets in Chronic Obstructive Pulmonary Disease **E. Papakonstantinou**
16:00 - 16:30	Obtaining information for the structure and function of CRF1 receptor to advance receptor-based drug design **G. Liapakis**
16:30 - 17:00	The role of nitric oxide donors in schizophrenia **N. Pitsikas**
17:00 - 17:30	Biological agents in rheumatic diseases **G. Vagiopoulos**
17:30 - 18:00	*Διάλειμμα Καφέ*
18:00 - 19:20	**Στρογγυλό Τραπέζι** ***Αντιβιωτικά*** **Προεδρείο: Μ. Μαρσέλος, Σ. Τσιάρα**
18:00 - 18:30	Νέα Αντιβιωτικά **Γ. Λιάμης**
18:30 - 18:50	Antibiotic Stewardship: Η διαχείριση των αντιβιοτικών στο νοσοκομειακό Περιβάλλον **Κ. Ιωαννίδης**
18:50 - 19:20	Antibiotic Stewardship: Τι έχει γίνει έως σήμερα στη χώρα μας; **Ε. Γιαμαρέλλου**

ΚΥΡΙΑΚΗ **27** ΜΑΪΟΥ **2018**

09:30 - 11:00 **Round table**
Molecular targets of new drugs against metabolic syndrome-related disorders (Part A)
Chairmen: I. Goudevenos, I. Andreadou

09:30 - 10:00 Targeting Glucose Transporter-4 (GLUT4) intrinsic activity for the development of a novel class of antihyperglycemic drugs
S. Sasson, *Israel*

10:00 - 10:30 New hypolipidemic drugs: PCSK9 inhibitors
M. Elisaf

10:30 - 11:00 HDL particle functionality as a novel pharmacological target in atherosclerosis and beyond
K. Kypreos

11:00 - 11:30 *Διάλειμμα Καφέ*

Παρουσίαση Αναρτημένων Ανακοινώσεων: Session B
PP29-PP56 *(σελ. 77-104)* *Εκθεσιακός Χώρος*

11:30 - 12:30 **Round table**
Molecular targets of new drugs against metabolic syndrome- related disorders (Part B)
Chairmen: G. Kolios, K. Kypreos

11:30 - 12:00 AMP-activated kinase (AMPK) in cardiovascular and metabolic disease: physiology, pharmacology and what lies beneath...
E. P. Daskalopoulos

12:00 - 12:30 New anticoagulants
S. Tsiara

12:30 - 13:30 *Μεσημεριανή Διακοπή - Ελαφρύ Σνακ*

Γενική Συνέλευση ΕΕΦ
Αίθουσα Lord Byron

13:30 - 15:15 Προφορικές Ανακοινώσεις/Oral Presentations SESSION B'

Προεδρείο: Χ. Λιάπη, Ε. Φριλίγγος *(σελ. 36-48)*

OP10

INVESTIGATING THE MOLECULAR MECHANISMS OF CARFILZOMIB-INDUCED CARDIOTOXICITY AND THE EMERGING ROLE OF METFORMIN AS A PROPHYLACTIC THERAPY

G. Kremastiotis[1], P. Efentakis[1], A. Varela[2], Ch. Davos[2], M. Tsoumani[1], E. D. Papanagnou[3], I. Trougakos[3], E.Kastritis[4], Z. Kanaki[2], E. Iliodromitis[5], A. Klinakis[2], M.Dimopoulos[4], E. Terpos[4], I. Andreadou[1]

[1]School of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece
[2]Biomedical Research Foundation Academy of Athens, Athens, Greece
[3]Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece
[4]Department of Clinical Therapeutics, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[5]2nd Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

OP11

NOVEL INDIRUBIN DERIVATIVES ATTENUATE INFARCT SIZE THROUGH GLYCOGEN SYNTHASE KINASE 3 BETA INHIBITION: THE EMERGING ROLE OF REGION SPECIFIC PHOSPHORYLATION BEYOND MPTP OPENING

P. E. Nikolaou[1], P. Efentakis[2], S. I. Bibli[3], K. Vougogiannopoulou[4], N. Gaboriaud-Kolar[1], V. Myrianthopoulos[1], N. Kostomitsopoulos[5], A. Leandros Skaltsounis[1], A. Papapetropoulos[1], E.K. Iliodromitis[6], I. Andreadou[1]

[1] National And Kapodistrian University of Athens, Athens, Greece
[2] Institute For Vascular Signalling, Centre For Molecular Medicine, Johann Wolfgang Goethe University, Frankfurt, Germany
[3] German Center of Cardiovascular Research (Dzhk), Partner Site Rhein-Main, Frankfurt Am Main, Germany
[4] Department of Pharmacognosy & Natural Products Chemistry, Faculty of Pharmacy, National And Kapodistrian University of Athens, Panepistimioupolis, 15771, Zografou, Athens, Greece
[5] Academy of Athens Biomedical Research Foundation, Centre of Clinical Experimental Surgery And Translational Research, Athens, Greece
[6] National And Kapodistrian University of Athens, Medical School, Attikon University Hospital, Athens, Greece

OP12

SERUM LEVELS OF IRISIN AND OMENTIN-1 ARE INCREASED IN PATIENTS WITH PROLIFERATIVE DISEASES OF THE BREAST. A POSSIBLE MECHANISM INVOLVING BREAST CANCER AND OBESITY?

G. Panagiotou[1], A. Vagionas[2], C. S. Mantzoros[3], E. Papakonstantinou[1]

[1] *Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece*
[2] *Theagenio Cancer Hospital, Thessaloniki, Greece*
[3] *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*

OP13

THE ANGIOGENESIS-RELATED EFFECTS OF HEALTHY DONOR-DERIVED HDL IN ENDOTHELIAL CELLS IN VITRO DEPEND ON NO PRODUCTION AND ACTIVATION OF KATP CHANNELS

Z. Panoutsopoulou[1], F. Kapoula[1], A. Pyriohou[1], E. Xepapadaki[2], G. Skroubis[3], K. Kypreos[2], S. Topouzis[1]
[1] *Department of Pharmacy, School of Health Sciences, University of Patras, Rio, Greece*
[2] *Department of Medicine, Pharmacology Laboratory, Panepistimioupolis, Rio, Greece*
[3] *Department of Surgery, Medical School, University of Patras Medical School, Rio, Greece*

OP14

THE IMPACT OF ESCALATING LOW-DOSE Δ9-THC DURING ADOLESCENCE ON PSYCHOTIC –LIKE SYMPTOMATOLOGY IN ADULT MALE RATS

N. Poulia[1], F. Delis[1], A. Polissidis[2], N. Kokras[3,4], C. Dalla[4], K. Antoniou[1]
[1] *Department of Pharmacology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece*
[2] *Laboratory of Neurodegenerative Diseases, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation Academy of Athens, Athens, Greece*
[3] *First Department of Psychiatry, Eginition Hospital, National and Kapodistrian University of Athens, Athens, Greece*
[4] *Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece*

OP15

THREE YEARS OF EXPERIENCE FROM USING GAME BASED LEARNING SOFTWARE FOR TEACHING AUTONOMOUS PHARMACOLOGY TO MEDICAL STUDENTS

C. Pourzitaki[1], L. Ioannidis[2], G. Papazisis[1], F. Malliou[1], T. Kirgidis[1], D. Kouvelas[1], P. Bamidis[1]
[1]*Laboratory of Clinical Pharmacology, School Of Medicine, Aristotle University of Thessaloniki, Greece*
[2]*Laboratory of Medical Physics, School Of Medicine, Aristotle University of Thessaloniki, Greece*

OP16

EFFECTS OF FOUR HERBAL EXTRACTS ON THE CHARACTERISTICS OF EPILEPTIFORM DISCHARGES IN CA1 PYRAMIDAL CELL LAYER OF RAT HIPPOCAMPAL SLICES

D. Kleidonas[1], A. Troganis[2], H. Stamatis[3], C. Psarropoulou[1]

[1] *Laboratory of Animal and Human Physiology, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece*
[2] *Laboratory of Environmental and Physical Chemistry Studies, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece*
[3] *Laboratory of Biotechnology, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece*

OP17

EFFECTS OF THE NOVEL DEHYDROEPIANDROSTERONE (DHEA) ANALOGUE BNN27 ON DIFFERENT ANIMAL MODELS OF SCHIZOPHRENIA

E. Zoupa[1], A. Gravanis[2], N. Pitsikas[1]
[1] *Department of Pharmacology, School of Medicine, University of Thessaly, Larissa, Greece*
[2] *Department of Pharmacology, School of Medicine, University of Crete, Heraklion, Greece*

OP18

SYNTHETIC MICRONEUROTROPHIN BNN27 AMELIORATES AMYLOID-BETA PATHOLOGY AND PROMOTES ADULT NEUROGENESIS IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE

K. Karali[1,2], M. Kokkali[1,2], P. Efstathopoulos[2], A. Gravanis[1,2], I. Charalampopoulos[1,2]
[1] *Institute of Molecular Biology and Biotechnology, Foundation of Research and Technology-Hellas (IMBB-FORTH), Heraklion, Greece*
[2] *Department of Pharmacology, School of Medicine, University of Crete, Heraklion, Greece*

OP19

EFFECTS OF RECEPTOR PROTEIN TYROSINE PHOSPHATASE BETA/ZETA INHIBITORS ON GLIOBLASTOMA CELLS AND ANGIOGENESIS

D. Spyropoulos[1], D. Denekou[1], S. Barmpoutsi[1], M. Drakopoulou[1], P. Castana[1], M. Pastor[2], G. Herradón[2], T. Tselios[3], E. Papadimitriou[1]
[1] *Department of Pharmacy, University Of Patras, Patras, Greece*
[2] *Facultad De Farmacia, Universidad San Pablo-Ceu, Ceu Universities Madrid, Spain*
[3] *Department of Chemistry, University Of Patras, Patras, Greece*

OP20

POTENTIAL ANTICANCER EFFECT OF ANTIPSYCHOTIC DRUGS: IN VITRO INVESTIGATION IN NSCLC CELL LINES

C.E. Andriopoulou, P. Kirgou, P. Pappas, G. Leondaritis, M. Konstandi
Department of Pharmacology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

OP21

SIGMA RECEPTORS EXPRESSION IN PANCREATIC CANCER AND EFFICACY EVALUATION OF THEIR LIGANDS USING COMPARE ALGORITHM AND PATIENT DERIVED XENOGRAFTS (PDX)

E. Sereti[1], C. Tsimplouli[1], T. Karagianellou[1], B. Cevatemre[2], E. Ulukaya[3], N. Sakellaridis[1], K. Dimas[1]

[1] Department of Pharmacology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

[2] Department of Biology, Faculty of Arts and Sciences, Uludag University, Bursa, Turkey

[3] Department of Clinical Biochemistry, Faculty of Medicine, Istinye University, Istanbul, Turkey

OP22

EVALUATION OF NOVEL NUCLEOSIDE ANALOGUES FOR LUNG CANCER TREATMENT: AN APPROACH BASED ON METRONOMIC CHEMOTHERAPY

E. Skavatsou, T. Karampelas, C. Tamvakopoulos

Biomedical Research Foundation, Academy of Athens, Center of Clinical Research, Experimental Surgery and Translational Research, Division of Pharmacology-Pharmacotechnology, Athens, Greece

15:15 - 16:45	**Round table** ***Recent advances in cancer therapy*** **Chairmen: G. Pentheroudakis, A. Chatzaki**
15:15 - 15:45	Igf1 alternative splicing: Ec role in prostate cancer biology and beyond **M. Koutsilieris**
15:45 - 16:15	Personalised anticancer therapy and liquid biopsies, present and future **G. Zarkavelis**
16:15 - 16:45	Applications of the CRISPR-Cas system in cancer therapeutics **A. Magklara**
16:45 - 17:00	*Διάλειμμα Καφέ*

17:00 – 18:10	**Διαλέξεις** **Προεδρείο: Λ. Σκαλτσούνης, Ν. Τσοπάνογλου**
17:00 - 17:30	Τα φυτικά προϊόντα ως μοχλός ανάπτυξης της χώρας - επιλεγμένα παραδείγματα **Ι. Χήνου**
17:30 - 17:50	Επιστημονική Αξιολόγηση Βιο-ομοειδών **Π. Τσαντίλη**
17:50 - 18:10	Κανονιστικό πλαίσιο βιο-ομοειδών στην Ευρώπη **Α. Ρομποτή**
18:10 - 19:15	***Βραβεύσεις Εργασιών***
19:15	**Λήξη Εργασιών**

ANDRE NICOLAS
Senior consultant, Pediatric Oncology AP-HM, Department of Hematology & Pediatric Oncology, "Hôpital pour Enfants de La Timone", Marseille, France

BRIZZI MARIA FELICE
Associate Professor of Internal Medicine, Department of Medical Sciences, University of Turin, Turin, Italy

SASSON SHLOMO
Professor of Pharmacology, Institute for Drug Research, Faculty of Medicine, Hebrew University, Jerusalem, Israel

SIEST SOFIA
Director of Research in INSERM, Director of UMR INSERM U1122, Director of BRC «Interactions Gθne-Environnement en Physiopathologie Cardio-Vasculaire» (IGE-PCV), Faculti de Pharmacie, Université de Lorraine, France

SIMMACO MAURIZIO
Professor of Molecular Biology, Department of Neurosciences, Mental Health and Sensory Organs, Faculty of Medicine and Psychology, Sant'Andrea Hospital – Sapienza University of Roma, Italy

ΑΝΔΡΕΑΔΟΥ ΙΩΑΝΝΑ
Αναπληρώτρια Καθηγήτρια Φαρμακολογίας, Εργαστήριο Φαρμακολογίας, Τομέας Φαρμακευτικής Χημείας,Τμήμα Φαρμακευτικής, Πανεπιστήμιο Αθηνών, Αθήνα

ΑΝΤΩΝΙΟΥ ΑΙΚΑΤΕΡΙΝΗ
Αναπληρώτρια Καθηγήτρια Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα

ΒΑΪΟΠΟΥΛΟΣ ΓΕΩΡΓΙΟΣ
Παθολόγος – Ρευματολόγος, Ομότιμος Καθηγητής, Ιατρική Σχολή, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα

ΓΙΑΜΑΡΕΛΛΟΥ ΕΛΕΝΗ
Παθολόγος-Λοιμωξιολόγος, Καθηγήτρια Παθολογίας, Ιατρική Σχολή, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών, Διευθύντρια, ΣΤ' Παθολογική Κλινική, Γενικό Νοσοκομείο Αθηνών "ΥΓΕΙΑ", Αθήνα

ΓΟΥΔΕΒΕΝΟΣ ΙΩΑΝΝΗΣ
Καθηγητής Παθολογίας - Καρδιολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Διευθυντής, Α' Καρδιολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων, Ιωάννινα

ΓΟΥΛΑΣ ΑΝΤΩΝΙΟΣ
Καθηγητής Φαρμακολογίας, Α' Εργαστήριο Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη

ΓΡΑΒΑΝΗΣ ΑΧΙΛΛΕΑΣ
Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Κρήτης, Κρήτη, Ερευνητής IMBB-FORTH

ΔΑΛΛΑ ΧΡΙΣΤΙΝΑ
Επίκουρη Καθηγήτρια Φαρμακολογίας, Ιατρική Σχολή, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών - Πρόεδρος, Ελληνική Εταιρεία για τις Νευροεπιστήμες, Αθήνα

ΔΑΣΚΑΛΟΠΟΥΛΟΣ ΕΥΑΓΓΕΛΟΣ Π.
RPh, PhD Post-Doctoral Research Fellow, Ptle de Recherche Cardiovasculaire (CARD), Institut de Recherche Expirimentale et Clinique (IREC), Université Catholique de Louvain (UCL), Brussels, Belgium

ΕΛΙΣΑΦ ΜΩΥΣΗΣ
Καθηγητής Παθολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Διευθυντής, Β' Παθολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων, Ιωάννινα

ΖΑΡΚΑΒΕΛΗΣ ΓΕΩΡΓΙΟΣ
Παθολόγος Ογκολόγος, Ογκολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων, Ιωάννινα

ΘΕΡΜΟΥ ΚΥΡΙΑΚΗ
Καθηγήτρια Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Κρήτης, Κρήτη

ΙΩΑΝΝΙΔΗΣ ΚΩΝΣΤΑΝΤΙΝΟΣ
Κλινικός Φαρμακοποιός MSc, PhD, Διαγνωστικό και Θεραπευτικό Κέντρο Αθηνών "ΥΓΕΙΑ", Αθήνα

ΚΑΡΑΚΙΟΥΛΑΚΗΣ ΓΕΩΡΓΙΟΣ
Καθηγητής Φαρμακολογίας, Εργαστήριο Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

ΚΟΛΙΟΣ ΓΕΩΡΓΙΟΣ
Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Δημοκρίτειο Πανεπιστήμιο Θράκης, Αλεξανδρούπολη

ΚΟΥΒΕΛΑΣ ΔΗΜΗΤΡΙΟΣ
Καθηγητής Κλινικής Φαρμακολογίας & Φαρμακολογίας, Διευθυντής, Εργαστήριο Κλινικής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη

ΚΟΥΤΣΙΛΙΕΡΗΣ ΜΙΧΑΗΛ
Καθηγητής Πειραματικής Φυσιολογίας και Διευθυντής Εργαστηρίου Φυσιολογίας, Ιατρική Σχολή, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών και Πρόεδρος του Ινστιτούτου Εφαρμοσμένης Φυσιολογίας και Άσκησης στην Ιατρική

ΚΥΠΡΑΙΟΣ ΚΥΡΙΑΚΟΣ
Καθηγητής Φαρμακολογίας, Διευθυντής Εργαστηρίου Φαρμακολογίας Τμήματος Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Πατρών, Πάτρα

ΚΩΝΣΤΑΝΤΗ ΜΑΡΙΑ
Καθηγήτρια Φαρμακολογίας, Διευθύντρια Εργαστηρίου Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα

ΛΕΟΝΤΑΡΙΤΗΣ ΓΕΩΡΓΙΟΣ
Επίκουρος Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα

ΛΙΑΜΗΣ ΓΕΩΡΓΙΟΣ
Αναπληρωτής Καθηγητής Παθολογίας, Β' Παθολογική κλινική, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα

ΛΙΑΠΑΚΗΣ ΓΕΩΡΓΙΟΣ
Αναπληρωτής Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Κρήτης, Κρήτη

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Καθηγήτρια Φαρμακολογίας , Εργαστήριο Φαρμακολογίας, Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα

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ΜΑΝΩΛΟΠΟΥΛΟΣ ΕΥΑΓΓΕΛΟΣ
Καθηγητής Φαρμακολογίας, Διευθυντής Εργαστηρίου Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Δημοκρίτειο Πανεπιστήμιο Θράκης, Αλεξανδρούπολη

ΜΑΡΣΕΛΟΣ ΜΑΡΙΟΣ
Ομότιμος Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα

ΝΙΚΟΛΑΪΔΗ ΕΛΕΥΘΕΡΙΑ
Φαρμακοποιός PhD, Κλινική Αξιολογήτρια, Διεύθυνση Αξιολόγηση Προϊόντων, Εθνικός Οργανισμός Φαρμάκων

ΝΟΜΙΚΟΣ ΓΕΩΡΓΙΟΣ
Dr., CNS Clinical Drug Development, Biogen, Global Medical Lead, Cambridge, MA

ΠΑΠΑΔΗΜΗΤΡΙΟΥ ΕΥΑΓΓΕΛΙΑ
Καθηγήτρια Μοριακής Φαρμακολογίας, Τμήμα Φαρμακευτικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Πατρών, Πάτρα

ΠΑΠΑΖΟΓΛΟΥ ΑΓΑΜΕΜΝΩΝ
Investment Manager, Charamida Investment Group, ELPEN group

ΠΑΠΑΚΩΝΣΤΑΝΤΙΝΟΥ ΕΛΕΝΗ
Καθηγήτρια Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη

ΠΑΠΑΠΕΤΡΟΠΟΥΛΟΣ ΑΝΔΡΕΑΣ
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Αναπληρωτής Καθηγητής Φαρμακογονιδιωματικής και Φαρμακευτικής Βιοτεχνολογίας, Εργαστήριο Φαρμακογονιδιωματικής και Εξατομικευμένης Θεραπείας, Τμήμα Φαρμακευτικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Πατρών, Πάτρα, Τακτικό Μέλος και Εθνικός Εκπρόσωπος, CHMP Pharmacogenomics Working Party, Ευρωπαϊκή Υπηρεσία Φαρμάκων, Λονδίνο

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Αναπληρωτής Καθηγητής Ογκολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Διευθυντής, Ογκολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων, Ιωάννινα

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Αναπληρωτής Καθηγητής Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Θεσσαλίας, Λάρισα

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Καθηγητής Φαρμακογνωσίας, Διευθυντής, Εργαστήριο Φαρμακογνωσίας και Χημείας Φυσικών Προϊόντων, Τμήμα Φαρμακευτικής, Σχολή Επιστημών Υγείας, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα

ΣΩΤΗΡΟΠΟΥΛΟΣ ΙΩΑΝΝΗΣ
Group Leader, ICVS Institute, Medical School, University of Minho, Portugal

ΤΑΥΡΙΔΟΥ ΑΝΝΑ
Αναπληρώτρια Καθηγήτρια Φαρμακολογίας, Τμήμα Ιατρικής, Δημοκρίτειο Πανεπιστήμιο Θράκης, Αλεξανδρούπολη, Εθνικός Εμπειρογνώμονας, Ευρωπαϊκός Οργανισμού Φαρμάκου

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Καθηγήτρια Ανατομίας, Ιατρική Σχολή, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα

ΤΡΥΦΩΝ ΘΕΟΔΩΡΟΣ
Πρόεδρος, Πανελλήνια Ένωση Φαρμακοβιομηχανίας (ΠΕΦ)

ΤΣΑΝΤΙΛΗ ΠΑΝΑΓΙΩΤΑ
Δρ. φαρμακοποιός, Αξιολογήτρια, Τμήμα Αξιολόγησης Βιολογικών Προϊόντων, Διεύθυνση Αξιολόγησης Προϊόντων, Εθνικός Οργανισμός Φαρμάκων

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Καθηγητής Φαρμακολογίας, Εργαστήριο Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Πατρών, Πάτρα

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Καθηγητής Βιολογικής Χημείας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα

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Καθηγήτρια Φαρμακολογίας, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Δημοκρίτειο Πανεπιστήμιο Θράκης, Αλεξανδρούπολη

ΧΗΝΟΥ ΙΩΑΝΝΑ
Καθηγήτρια Φαρμακογνωσίας και Χημείας Φυσικών Προϊόντων, Τμήμα Φαρμακευτικής, Σχολή Επιστημών Υγείας, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα

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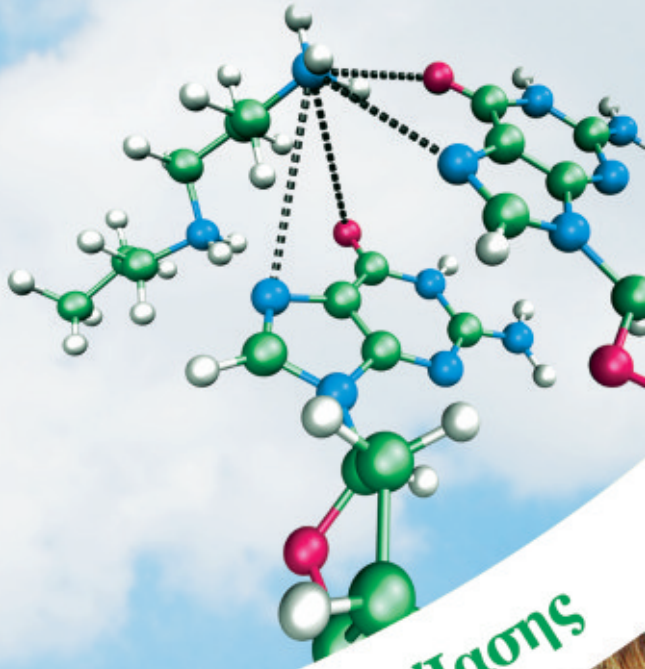

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Προφορικές Ανακοινώσεις/Oral Presentations SESSION A'

OP1

A CRITICAL RE-EVALUATION OF FIRST-GENERATION VANADIUM-BASED PTEN INHIBITORS IN VIVO

G. Aggelis[1], M. Papanikolaou[2], C.E. Andriopoulou[1], B.J Eickholt[3], M. Konstandi[1], T.A. Kabanos[2], G. Leondaritis[1]

[1] Laboratory Of Pharmacology, Medical School, University Of Ioannina, Ioannina, Greece

[2] Section Of Inorganic And Analytical Chemistry, Department Of Chemistry, University Of Ioannina, Ioannina, Greece

[3] Institute Of Biochemistry, Charite-Universitatsmedizin Berlin, Neurocure Cluster Of Excellence, Berlin, Germany

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a pleiotropic and multimodal phosphoinositide/protein phosphatase crucially positioned at the intersection of signalling pathways that regulate cellular metabolism, growth, and survival. In recent years, it has become apparent that PTEN constitutes a functionally dual "yin-yang" protein with high potential for pharmacological targeting that may be clinically useful in certain settings. Accordingly, compounds that are purported to act as PTEN inhibitors have shown promising results in enhancing functional recovery after nerve, lung, or cardiac injury in cell-based and animal models.

Aim: First-generation PTEN inhibitors, particularly bisperoxo-vanadium (bpV) and oxo-vanadium (VO) complexes with bulk organic ligands were originally demonstrated to display variable PTEN selectivity in vitro. In vivo, significant efficacy in nerve and cardiac injury animal models was associated with activation of growth-promoting PI3K/Akt/GSK3 and mTORC1-dependent signalling pathways. However, recent studies have questioned their PTEN specificity and selectivity over protein tyrosine kinases as well as their mechanism of action. Here, we have embarked on a systematic pharmacological characterization of the action of a series of standard and novel bpV and VO compounds.

Methodology-Results-Conclusions: We have verified PTEN inhibition in vitro as well as the upregulation of phospho-Ser473-Akt, phospho-Ser9-GSK3 and phospho-Ser235/236-S6 levels upon short-term incubation with low micromolar concentrations of bpV(phen), bpV(OHpic) and VO(OHpic), indicating robust activation of Akt/GSK3β and mTORC1 signalling in cells. In sharp contrast, bpV(bipy), although very similar to bpV(phen) and a potent PTEN inhibitor in vitro, was largely inactive in this assay. Dose-response experiments with bpV(phen) showed that Akt phosphorylation was increased in a dose-dependent manner with an EC50 value of approx. 4 μM. Interestingly, this dose-dependent increase in Akt phosphorylation was abolished in PTEN-null cells, suggesting that PTEN is the primary target of bpV(phen). In our ongoing experiments we utilize a battery of assays in order to re-evaluate and refine the selectivity and mechanism(s) of action of these first-generation PTEN inhibitors in cells. Our long-term goal is to develop novel, specific, PTEN inhibitors and in parallel define the attributes and desirable properties of a safe PTEN inhibitor in vivo.

OP2

A NOVEL MODULATOR OF AMPA RECEPTORS AGAINST ALZHEIMER'S DISEASE PATHOLOGY: THE FIRST IN VIVO EVIDENCE

D. Monteiro[1], J. M. Silva[1], S. Ferreira[1], C. Soares-Cunha[1], S. Bretin[2], N. Sousa[1], I. Sotiropoulos[1]

[1] Life And Health Sciences Research Institute (Icvs), School Of Health Sciences, University of Minho, Braga, Portugal, Icvs/3b's–Pt Government Associate Laboratory, Braga/Guimaryes, Portugal

[2] 3ptle Innovation Thırapeutique Neuropsychiatrie, Institut De Recherches Internationales Servier, Suresnes, France

Alzheimer's disease (AD), the most prevalent form of dementia affecting approximately 43 million people worldwide, represents a priority public health problem according to World Health Organization 2017-2025 plan. Despite the considerable progress in understanding the neuropathology of the disease, AD remains a complex disorder with undefined initiators and no effective treatment that can block APP misprocessing and Tau hyperphosphorylation, the two AD neuropathological mechanisms. Mounting evidence suggest a precipitating role for environmental stress and glutamate signaling in AD while glutamate receptor signaling has been suggested as a therapeutic target against AD synaptic pathology. Hereby, we evaluate the effects of a modulator of AMPA receptor(AMPAR) on a combined rat model of stress/Aβ-driven AD. We have used a chronic unpredictable stress protocol, over 4 weeks, followed by osmotic pump implantation, to deliver either $A\beta_{1-40}$ or saline (control), while chronic administration of AMPAR at 3 and 10mg/kg followed. Two-way ANOVA analysis revealed no differences of total distance travelled in the Open Field arena indicating no locomotion differences among animal groups. In Elevated Plus Maze test, the stress/Aβ animal group showed a decrease in the time as well as in the entries in the open arms, that was not reverted upon treatment with AMPAR, suggesting that this compound does not exhibit an anxiolytic effect. In contrast, the stress/Aβ animals presented short and long-term memory deficits in Novel Place and Object Recognition tasks. Interestingly, the above memory deficits were blocked upon treatment with AMPAR with its effect being more pronounced at 10mg/kg dose. In addition, stress/Aβ animals exhibited increased swim distance in Morris Water Maze task indicating cognitive deficits that was also reverted upon chronic treatment with AMPAR. No differences were found in any of the behavioral tasks/tests when control animals treated with 3 and 10mg/kg AMPAR. Our findings demonstrated that AMPAR compound reverted both recognition and spatial memory deficits in this AD animal model suggesting a beneficial effect of hippocampus- and prefrontal-cortex-dependent cognitive function. These studies constitute the first *in vivo* screening of this AMPA-related novel compound suggesting glutamatergic signaling as potential target against cognitive impairment in early-phases of Alzheimer's disease.

OP3

ALTERED ONE-CARBON PATHWAY BY DIETARY MODIFICATIONS DISRUPTSCARDIAC EXTRACELLULAR MATRIXHOMEOSTASIS AND IMPAIRS NORMAL HEART FUNCTION

A. Strilakou[1], I. Mourouzis[1], A. Lazaris[2], A. Al-Humadi[1], P. Karkakousos[3], C. Pantos[1], C. Liapi[1]

[1] Department of Pharmacology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[2] 1st Department of Pathology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[3] Department of Medical Laboratories, Technological Institute of Athens, Athens, Greece

Background: One-carbon (1C) metabolism, mediated mainly by folate, supports multiple physiological processes including amino acid homeostasis (glycine, serine and methionine), epigenetic maintenance, and redox defense.Choline is a B vitamin cofactor and its deficiency has been widely associated with increased oxidative stress and fatty liver disease. However, it is also implicated in the methionine-homocysteine cycle, which in turn is involved in the one carbon cycle. Matrix metalloproteinases (MMPs) are a family of latent zinc- and calcium-dependent enzymes responsible for extracellular matrix degradation. The disturbed balance between MMP-2, MMP-9 and their respective inhibitors TIMP-2, TIMP-1 has been involved in the pathogenesis of various cardiovascular disorders. The aim of the study was to investigate the effect of dietary choline deprivation on cardiac function and extracellular matrix homeostasis (ECM) in the absence of any underlying disease.

Materials and Methods: Male Wistar Albino adult rats were used and divided according to the diet they received; standard or choline-deficient. After four weeks of treatment, cardiac function wasassessed under isometric conditions using the Langendorff preparations [Left Ventricular Developed Pressure (LVDP-mmHg), positive and negative first derivative of LVDP were evaluated], serum homocysteine and brain natriuretic peptide (BNP) levels were measured and histopathology analyses with immunohistochemistry for MMP-2, MMP-9, TIMP-1, and TIMP-2 were performed.

Results: In the choline-deprived group a compromised myocardium contractility (P=0.01), as assessed by LVDP, was noted along with a significantly impaired diastolic left ventricular function, as assessed by (-) dp/dt (P=0.02) with increased BNP and homocysteine levels. Heart histopathology revealed a lymphocytic infiltration of myocardium and valves with suppressed immunohistochemical expression of MMP-2 and increased expression of TIMP-2. MMP-9 expression was decreased without, however, reaching statistical significance while there was no impact on TIMP-1.

Conclusions: Choline deficiency impairs heart mechanical properties and induces ECM dysregulation promoting fibrosis that lead to the establishment of a restrictivepattern with diastolic dysfunction. The clinical implications and the molecular underlying mechanisms need further investigation

OP4

MITOCHONDRIA AS PHARMACOLOGICAL TARGETS FOR ANXIETY AND STRESS-RELATED DISORDERS

M.D. Filiou

Department of Biological Applications and Technology, School of Health Sciences, University of Ioannina, Ioannina, Greece

Current treatments for anxiety and stress-related pathologies suffer from slow mode of action, severe side-effects and low remission rates. Elucidating the molecular underpinnings of stress-related and anxiety disorders is crucial for developing more effective therapies.
Here, we will present data from a series of mouse models of anxiety and stress-related phenotypes which were analyzed by combining state-of-the-art proteomic, metabolomic, bioinformatic, biochemical and pharmacological approaches.
We will show that in all mouse models studied, changes in synaptic mitochondria mediate anxiety and stress responses. These mitochondrial changes are linked to altered mitochondrial protein/gene expression, altered mitochondrial number and increased oxidative stress and are brain region specific. Following these results, we will then demonstrate that pharmacological manipulation of mitochondria in high anxiety exerts anxiolytic effects *in vivo*.
Finally, we will discuss whether brain mitochondria can be used as pharmacological targets and explore the therapeutic potential of selective mitochondrial targeting for anxiety and stress-related disorders.

OP5 *(θα παρουσιαστεί ως PP57 , Παρουσίαση Αναρτημένων Ανακοινώσεων: Session A)*

BNN27 EXERTS SIGNIFICANT ANTI-INFLAMMATORY EFFECTS ON T-LYMPHOCYTES DERIVED FROM MICE FOLLOWING CFA-INDUCED INFLAMMATION

S. Poulaki, M. Venihaki

Faculty of Medicine, School of Health Sciences, University of Crete, Heraklion, Greece

Aim of the study: During tissue injury or infection, leukocytes are activated to produce a variety of pro-inflammatory mediators such as cytokines (IL-6, TNF-α, IL-1β), growth factors, neuropeptides, prostaglandins, and chemokines which sensitize nociceptors and produce pain signals. The pro-inflammatory mediators trigger the immune system to produce and release anti-inflammatory and analgesic molecules such as anti-inflammatory cytokines and opioid peptides. Previous studies of our research team indicate that microneurotrophins such as the spriro-epoxy derivative of DHEA, BNN27, exert significant analgesic and anti-inflammatory effects during inflammation-induced analgesia produced by Complete Freund's Adjuvant (CFA). Based on the above, the aim of the present study was to examine the effect of BNN27 on T-lymphocytes isolated from mice injected with CFA.

Methods: Male and/or female wild type mice with C57BL6x1291Sv genetic background were injected with 20μl of CFA on their left hind paw to induce inflammation and hyperalgesia. Six hours following the induction of inflammation, spleens were collected in sterile ice cold PBS and smashed using the rough side of frosted glass slides. Lymphocytes were collected using ammonium chloride solution and placed in culture with RPMI medium containing FBS, antibiotics, sodium pyruvate, concanavalin-A and IL-2 to prompt T-lymphocyte proliferation and differentiation. Cells were then treated with BNN27 at 10^{-6}, 10^{-7}, and 10^{-8} M and the culture media and the cells were collected at 3, 6 and 24 hours for ELISA and PCR assays. The proliferation rate of T-cells was also examined using the MTT assay at 24, 48, 72 and 96 hours following BNN27 treatment at the same concentrations.

Results: Our results showed that BNN27 at 10^{-8} M increased the proliferation of T-lymphocytes at 24 hours. In addition, BNN27 at the same concentration significantly decreased IL-6 and TNF-α protein levels at 6 hours, while it increased the mRNA expression of μ-opioid receptor and opioid peptides PENK and POMC at different time points.

Conclusions: Our data demonstrate considerable anti-inflammatory and analgesic effects of BNN27, making it a promising molecule for inflammation and pain management.

OP6

CIRCULATING CELL-FREE DNA IN BREAST CANCER: A VALUABLE TOOL FOR PROGNOSIS AND PREDICTION OF TREATMENT RESPONSE

M. Panagopoulou[1], M. Karaglani[1], I. Balgkouranidou[1], V. Vasilakakis[2], E. Biziota[1], T. Koukaki[1], E. Karamitrousis[1], E. Nena[1], I. Tsamardinos[2], G. Kolios[1], S. Kakolyris[1], E. Chatzaki[3]

[1] Medical School, Democritus University Of Thrace, Alexandroupoli, Greece
[2] Department Of Computer Science & Gnosis Data Analysis, University Of Crete, Voutes, Greece
[3] Medical School, Democritus University Of Thrace, Alexandroupolis Greece & Foundation of Research And Technology Hellas, Voutes, Crete

Aim: The characterization of circulating cell-free DNA (ccfDNA) in terms of methylation patterns, levels and origin is pointing to a potentially valuable minimally invasive tool for cancer prognosis and monitoring. Here, we analyzed the methylation pattern of a panel of cancer-related genes, considered as clinically significant based on previous expression and epigenetic data. Also, we evaluated levels and fragment size distribution of ccfDNA. Adjuvant, metastatic and neo-adjuvant patients were employed in the study and findings were associated to their disease characteristics and follow-up data.

Methods: Plasma cfDNA from 35 healthy volunteers, 150 and 16 breast cancer patients under adjuvant and neoadjuvant therapy respectively and 34 patients with metastatic disease was directly quantified using a fluorometer and then isolated. The size of extracted ccfDNA was analyzed by capillary electrophoresis. Promoter methylation status of 5 genes (*GATA3, MSH2, KLK10, SOX17, WNT5A*) was assessed by quantitative methylation specific PCR (QMSP). Statistical analysis revealed correlations to clinical end points. The JAD Bio toolkit was used to highlight signatures with prognostic value.

Results: Different percentages and levels of methylation was found in all patient groups for all genes, higher that the helthy volunteer control group. In the adjuvant group, Kaplan-Maier showed that patients who had methylated the *KLK10* gene had shorter disease free interval (DFI) (*p<0.013*). Also, metastatic patients who had higher ccfDNA levels had shorter progression free survival (PFS) (*p<0.036*) and overall survival (OS) (*p=0.003*). In the same group, those who had *SOX17, WNT5A* or at least 3 genes methylated, had shorter OS (*p=0.042, p=0.043 and p=0.048* respectively). Then, specific signatures were highlighted which contained combined significant features for prognosis and treatment response prediction.Average plasma cfDNA concentrations were found higher in patient groups, than in the group of healthy volunteers. The preliminary data of the fragment size evaluation showed a wider fragment distribution of ccfDNA in breast cancer patients, indicating release during different cellular processes.

Conclusion: Our results showed correlations of ccfDNA levels and patterns on gene methylation detected there with disease prognostic parameters and DFI. The signatures that developed could be a powerful tool for breast cancer prognosis and treatment selection.

OP7

EFFECTS OF IMATINIB AND DICHLOROACETATE ACID ON CELLULAR BIOENERGETICS OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

D. Mavridou, G. Gavriilidis, L. Papadopoulou

Laboratory of Pharmacology, Faculty of Pharmacy, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

Objectives: Oxidative phosphorylation (OxPhos) and glycolysis are the main pathways for energy production in mammalian cells (bioenergetics). Because malignant transformation is interweaved with metabolic reprograming, these two pathways stand at the epicenter of modern cancer pharmacology. Chronic Lymphocytic Leukemia (CLL) is characterized by the clonal expansion and accumulation of mature B lymphocytes in the peripheral blood and secondary lymphoid organs. In CLL, some patients survive without any treatment for many years, others develop a rapidly fatal disease despite the implementation of aggressive therapeutic protocols. CLL cells are characterized by metabolic plasticity, promoting cancer progression, resistance to chemotherapy and poor survival.

Previous work from our group has shown that Imatinib mesylate (IM/Gleevec®), a selective inhibitor of chimeric Bcr-Abl tyrosine kinase, disrupts the cytochrome c oxidase (COX) biosynthesis and assembly pathway, indicating that this agent negatively modulates OxPhos in Bcr-Abl(+) Chronic Myeloid Leukemia (CML) cells. Extending our research in CLL [Bcr-Abl(-)], we investigated the effects both of IM plus Dichloroacetic acid (DCA), a known inhibitor of glycolysis.

Materials-methods: MEC-1 CLL cells, with a doubling time of ~40hr, were treated with various concentrations of IM (1-2 μM) and DCA (1,2,4 mM) at different time-points (24-96 hr) and assessed for viability and expression of multiple proteins implicated in cellular bioenergetics.

Results: Our experimental data obtained thus far show that: **a)** IM and DCA, added separately as well as in combination, inhibit the viability of CLL cells; and **b)** IM and DCA affect the profile of expression of a number of different proteins involved in glycolysis, OxPhos, hypoxic cellular adaptation and generation of reactive oxygen species. More specifically: **i)** IM reduced the expression of most proteins examined (like Sco2, HO-1, VEGFc, GAPDH, Hif-1a, NF-kB); **ii)** DCA increased the expression of Sco2, HO-1, VEGFc, GAPDH, while reduced that of Hif-1a and NF-kB; and**iii)** co-administration of IM/DCA reduced, to a greater extent, the expression of both Hif-1a and NF-kB.

Discussion: These findings advocate that hijacking the intricate metabolic plasticity of CLL cells can pave the way for novel therapeutic approaches, especially for patients with poor clinical outcome or with resistance to current, clinically available pharmaceuticals.

OP8

TRIANGULATING BETWEEN DRUG, GENES AND PHARMACOGENOMIC BIOMARKERS TO CLINICALLY IMPLEMENT PRECISION MEDICINE

S. Koutsilieri, G. Patrinos

University of Patras School of Health Sciences, Department of Pharmacy, Laboratory of Pharmacogenomics and Individualized Therapy, Patras, Greece

Aim of the study: Pharmacogenomics aims to rationalize drug use by minimizing drug toxicity and/or by increasing drug efficacy. To date, over 150 drugs have been approved by the US Food and Drug Administration and the European Medicines Agency bearing pharmacogenomics information in their labels, bringing precision medicine closer to clinical fruition. However, no comprehensive lists exist online, for clinicians to retrieve the information related to the respective pharmacogenomic biomarkers, allowing them to rationalize drug treatment for their patients.

Methods: In order to create such comprehensive resource, we have extracted and curated information from the published literature and online resources, such as the Clinical Pharmacogenomics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledgebase (PharmGKB), which includes the level of evidence (A-D for CPIC and 1A-4 for PharmGKB), also in line of the existing information documented in the major regulatory bodies, such as the US Food and Drug Administration and the European Medicines Agency.

Results: We have identified 226 drugs that correlate with 95 genes, resulting in 294 recommendations for drug treatment modalities. From these recommendations, 103 relate to the development of drug toxicity (e.g. adverse drug reactions), 123 relate to lack of efficacy, 45 correspond to both cases (that is lack of efficacy and development of drug toxicity), while 23 are for information only.

Conclusions: This comprehensive list would be readily applicable to develop an online resource catalyzing the application of clinical pharmacogenomics while it stands as the first example of an one-stop solution to assess in real-time the implication of genomic biomarkers in drug response, leading to treatment individualization.

[#] SK is a recipient of an Onassis Foundation scholarship.

OP9

EFFECT OF EBSELEN ON CENTRAL 5-HT2A RECEPTOR FUNCTION AND EXTRACELLULAR 5-HT IN THE MOUSE

I. Antoniadou[1,2], M. Kouskou[2], T. Arsiwala[2], N. Singh[2], S. Vasudevan[2], G. Churchill[2], T. Sharp[2]

[1] *Department of Pharmacy, School of Life Sciences, European University of Cyprus, Cyprus*
[2] *Department of Pharmacology, University of Oxford, Oxford, UK*

Inhibition of inositol monophosphatase (IMPase) and decreased phosphoinositide (PI) signalling may underlie the mood stabilising actions of lithium (Berridge et al., 1989). We have shown that ebselen inhibits IMPase and attenuates amphetamine-induced hyperactivity, similarly to lithium (Singh et al., 2013). Here, we studied the effect of ebselen and lithium on 5-HT2A receptor, which is Gq coupled to PI signalling. Given that reduced 5-HT2A receptor function is a common effect of antidepressants, we also studied the effect of ebselen, alone and in combination with an SSRI, on brain extracellular 5-HT.

Adult male C57BL/6 mice were treated with vehicle, ebselen (1, 5 or 10 mg/Kg) or lithium (acutely: 10 mmol/Kg; or repeatedly: first dose 10 mmol/Kg then 3 mmol/Kg twice daily for 3 or 7 days) followed 1 h later by the non-selective 5-HT2A receptor agonist DOI (2 mg/Kg). DOI-induced head twitch responses (HTR) and ear scratch responses (ESR) were scored for 15 min. DOI-induced c-fos mRNA was also measured in mice pretreated with either ebselen (10 mg/Kg) or lithium (7 days). *In situ* hybridization was performed on brain sections using ^{35}S-dATP labelled oligonucleotides complimentary to *c-fos* mRNA. For extracellular 5-HT, mice were treated with vehicle or ebselen (10 mg/Kg) followed 1 h later by vehicle or citalopram (5 mg/Kg). Hippocampal dialysates were collected every 20 min for 2 h and 5-HT was measured with HPLC coupled to electrochemical detector. Data were analysed statistically using Student's unpaired t-test or one way ANOVA with post hoc LSD as appropriate (n=6-8 per group).

Compared to vehicle controls, ebselen dose-dependently decreased both HTR and ESR elicited by DOI. Acute lithium also decreased the ESR while repeated lithium decreased both the ESR and HTR. DOI-induced *c-fos* mRNA was decreased by ebselen in cortical regions. Repeated lithium also reduced the *c-fos* response to DOI. Additionally, ebselen enhanced citalopram-induced increase in extracellular 5-HT in hippocampus.

Overall, ebselen attenuated 5-HT2A receptor function, in a fashion similar to lithium. Also, ebselen augmented the effects of citalopram on extracellular 5-HT. This evidence adds further support to the clinical testing of ebselen in mood disorders, including as an antidepressant augmenting agent.

OP10

INVESTIGATING THE MOLECULAR MECHANISMS OF CARFILZOMIB-INDUCED CARDIOTOXICITY AND THE EMERGING ROLE OF METFORMIN AS A PROPHYLACTIC THERAPY

G. Kremastiotis[1], P. Efentakis[1], A. Varela[2], Ch. Davos[2], M. Tsoumani[1], E. D. Papanagnou[3], I. Trougakos[3], E.Kastritis[4], Z. Kanaki[2], E. Iliodromitis[5], A. Klinakis[2], M.Dimopoulos[4], E. Terpos[4], I. Andreadou[1]

[1]School of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece
[2]Biomedical Research Foundation Academy of Athens, Athens, Greece
[3]Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece
[4]Department of Clinical Therapeutics, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[5]2nd Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Aim: Carfilzomib (Cfz) is an irreversible proteasome inhibitor, indicated for the treatment of relapsed/refractory multiple myeloma (R/R MM) which has been associated with severe cardiotoxicity elicited through unknown mechanism. Aim of this study was to investigate i) the molecular mechanisms of Cfz-induced cardiotoxicity and ii) to investigate the cardioprotective effect of metformin (Met) against cardiotoxicity.

Methods: Male C57BL/6 mice, were randomized into Protocol 1: Control (N/S 0.9%, n=7) and Cfz group (n=8); Protocol 2: Control (N/S 0.9%, n=8); Cfz (n=8) and Cfz+Met (n=10). Cfz (8 mg/kg ip) was administered every 48h and Met (140 mg/kg po) every 24h for 6 days. Fastening glucose levels and cardiac function were monitored. Myocardial tissue samples were obtained for the analysis of proteasome peptidases activity, PP2A activity and molecular signaling mechanisms.

Results: Administration of Cfz resulted in significant reduction of the chymotrypsin-like proteasome activity in myocardial tissue and peripheral blood mononuclear cells of Cfz-treated mice vs. controls ($p<0.01$). Protocol 1: Cfz group had a significant decrease in FS% vs. Control at day 6 (39.87±0.47% vs. 42.05±0.64% respectively, $p<0.05$). Cfz increased PP2A activity vs. Control ($p<0.05$), without altering PP2A expression. A decrease in pAkt/tAkt ($p<0.05$), peNOS/teNOS ($p<0.05$), pAMPKα/tAMPKα ($p<0.001$) and an increase in the expression of iNOS ($p<0.01$) was observed in the Cfz group vs. Control. Protocol 2: Met did not reduce fastening glucose levels in Cfz+Met compared to Control and Cfz groups (102.4±5.9mmol/L vs. 114.3±13.9mmol/L and 118.1±8.2mmol/L, respectively). Echocardiographic assessment at day 6 revealed that Met reversed Cfz-induced reduction in the FS% in Cfz+Met vs. Cfz group (43.4±0.5% vs. 41.5±0.4% respectively, $p<0.05$). AMPKα phosphorylation was significantly increased in the same group compared to Cfz group ($p<0.01$).

Conclusion: Cfz induces cardiac dysfunction via increasing PP2A activity, leading to decreased phosphorylation of Akt, eNOS and AMPKα. The disturbance of Akt/AMPKα/eNOS axis and the increase of iNOS, suggests that Cfz might intervene with oxidative stress, apoptosis and myocardial energetic pathways. Therefore, Cfz-induced increase in PP2A activity seems to be essential in the mechanism of cardiotoxicity. Met restored AMPKα phosphorylation and reversed Cfz-induced contractile dysfunction, emerging to be a potent pharmacological intervention for the management of Cfz-induced cardiotoxicity.

OP11

NOVEL INDIRUBIN DERIVATIVES ATTENUATE INFARCT SIZE THROUGH GLYCOGEN SYNTHASE KINASE 3 BETA INHIBITION: THE EMERGING ROLE OF REGION SPECIFIC PHOSPHORYLATION BEYOND MPTP OPENING

P. E. Nikolaou[1], P. Efentakis[2], S. I. Bibli[3], K. Vougogiannopoulou[4], N. Gaboriaud-Kolar[1], V. Myrianthopoulos[1], N. Kostomitsopoulos[5], A. Leandros Skaltsounis[1], A. Papapetropoulos[1], E.K. Iliodromitis[6], I. Andreadou[1]

[1] National And Kapodistrian University of Athens, Athens, Greece

[2] Institute For Vascular Signalling, Centre For Molecular Medicine, Johann Wolfgang Goethe University, Frankfurt, Germany

[3] German Center of Cardiovascular Research (Dzhk), Partner Site Rhein-Main, Frankfurt Am Main, Germany

[4] Department of Pharmacognosy & Natural Products Chemistry, Faculty of Pharmacy, National And Kapodistrian University of Athens, Panepistimioupolis, 15771, Zografou, Athens, Greece

[5] Academy of Athens Biomedical Research Foundation, Centre of Clinical Experimental Surgery And Translational Research, Athens, Greece

[6] National And Kapodistrian University of Athens, Medical School, Attikon University Hospital, Athens, Greece

Purpose: The role of glycogen synthase kinase 3 beta(GSK3β) in cardioprotection and the link between GSK3β and the mitochondrial Permeability Transition Pore (mPTP)are debated. The aim of the study was: I. Investigate the pharmacological inhibition and GSK3βphosphorylation in cardioprotection II. Examine the direct effect of GSK-3β inhibitors on mPTP opening III. Define localization of GSK3β on normoxic and ischemic heart.

Materials and methods: The GSK3 inhibitor BIO and four novel analogues (MLS2776-MLS2779) were administered at the 20min of ischemia(I) in a rabbit model of 30min I- 3h reperfusion(R) and infarct size (IS) was determined. GSK3β inhibitory phosphorylation (S9) was examined at a second series of experiments at the 10th min of R. C57BL/6 mice subjected to 30' I/2h R randomly received vehicle, MLS2776 or MLS2778 (the most potent compounds) at the 20th min of I and IS was determined. In a second series of experiments, myocardial tissue was obtained at the 10thminute of R in order to investigate GSK3β inhibition. Additionally, an mPTP inhibitor, cyclosporine (CsA)(10mg/kg), MLS2776+CsA and MLS2778+CsA were administered for determination of IS. In order to address the GSK3β-mitochondria interaction, mice were either sham operated or subjected to 30'I/10'R and myocardial mitochondria were isolated and treated with the compounds for Calcium Retention Capacity (CRC) assay. GSK3β localization in the cytosolic and mitochondrial fractions was determined.

Results: All MLS analogues reduced IS compared to control in rabbits (10.6 ± 3.0%, 26.9 ± 2.9%,10.1 ± 1.5%,28.5 ± 4.0% vs 51.9 ± 2.5%, $p<0.001$). MLS2776 and MLS2778 reduced IS in mice (15.32±1.39% and 16.18± 1.91% vs 45.12±2.14%, $p<0.05$) and possessed an additional effect when co-administered with CsA indicating a different mechanism of action than CsA (10.23±0.47%, 11.17±0.76% vs 25.03±1.03% for CsA $p<0.05$). GSK3β inhibition was confirmed by a decrease in p(Tyr216)-GSK3β and p(Ser33/37/Thr41)-βcatenin($p<0.05$), but not by a p(Ser9)-GSK3β increase. CRC was not altered under normoxic and I/R conditions and GSK3β was primarily located in the cytosol.

Conclusions: Pharmacological inhibition of GSK3β attenuates IS beyond mPTP inhibition. However, a direct interaction of GSK3β and mPTP cannot be established and downstream cascade of GSK3β besides mPTP inhibition will be further investigated.

OP12

SERUM LEVELS OF IRISIN AND OMENTIN-1 ARE INCREASED IN PATIENTS WITH PROLIFERATIVE DISEASES OF THE BREAST. A POSSIBLE MECHANISM INVOLVING BREAST CANCER AND OBESITY?

G. Panagiotou[1], A. Vagionas[2], C. S. Mantzoros[3], E. Papakonstantinou[1]

[1] Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] Theagenio Cancer Hospital, Thessaloniki, Greece

[3] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Objective: The continuously increasing rates of cancer of different origins, including breast cancer, have been associated with the modern epidemic of obesity. One of the suggested mechanisms involved is the effect of adipose- or muscle- derived molecules, like omentin-1 and irisin, that are altered in obesity state. In this study, we aimed to evaluate serum irisin and omentin-1 levels in patients with breast proliferative diseases.

Patients- Methods: We recruited female patients with histologically proven benign (N=57), or with recently diagnosed treatment-naove malignant breast lesions (N=72), as well as healthy controls (N=56). Anthropometric, demographical and biochemical data were individually recorded. Body composition was evaluated by Bioelectrical Impedance. Serum levels of irisin and omentin-1 were quantified in early morning blood samples by ELISA.

Results: Analyzing the anthropometric, demographical and biochemical data of the subjects included in our study, we found that patients in the malignant group were older compared to benign group and to healthy group ($p<0.05$ for both comparisons) and had higher glucose levels and total body fat compared to healthy controls ($p<0.05$ for both comparisons). Irisin and omentin-1 serum levels were significantly increased in the benign group and in the malignant group, as compared to the healthy group ($p<0.001$ for all comparisons). Post-hoc Bonferroni analysis revealed that the observed increase of irisin and omentin-1 in the benign and malignant groups remained significant after adjusting for age, blood glucose and body mass index ($p=0.001$ for irisin, $p=0.004$ for omentin).

Conclusions: Irisin and, to a lesser extent, omentin-1 may be implicated in breast tumorigenesis and may explain the epidemiological connection of obesity with breast cancer development at a molecular level. These molecules could be used as non-invasive biomarkers for the diagnosis and/or prognosis of breast malignancy, as well as novel therapeutic targets. Our observations need to be validated in larger, prospective studies and future clinical trials.

OP13

THE ANGIOGENESIS-RELATED EFFECTS OF HEALTHY DONOR-DERIVED HDL IN ENDOTHELIAL CELLS IN VITRO DEPEND ON NO PRODUCTION AND ACTIVATION OF KATP CHANNELS

Z. Panoutsopoulou[1], F. Kapoula[1], A. Pyriohou[1], E. Xepapadaki[2], G. Skroubis[3], K. Kypreos[2], S. Topouzis[1]

[1] Department of Pharmacy, School of Health Sciences, University of Patras, Rio, Greece

[2] Department of Medicine, Pharmacology Laboratory, Panepistimioupolis, Rio, Greece

[3] Department of Surgery, Medical School, University of Patras Medical School, Rio, Greece

The physiological role of High Density Lipoprotein (HDL) is considered beneficial for health. However, it has been recently understood that HDL is highly heterogenous and that different species of HDL exhibit different anti-inflammatory and angiogenesis-related properties. Despite previous reports that HDL supports angiogenesis, the molecular mechanisms implicated are poorly characterized. Angiogenesis is a vital process in tissue growth, development, wound healing and cancer growth, therefore understanding how HDL can influence it has wide implications. The aim of this study was to a) better characterize the molecular pathways contributing to angiogenesis induced by healthy donor HDL, and b) compare the angiogenic potential of HDL from healthy individuals and morbidly obese patients, before and after gastric bypass surgery performed on the latter. To accomplish this, we determined the effects of HDL *in vitro*, in three different cellular processes critical for angiogenesis, using Human Umbilical Vein Endothelial Cells (HUVECs, passages 1-4): 1) cell proliferation (assessed by determination of cell number), 2) cord-like network formation in Matrigel (assessed by total network length), and 3) scratch wound healing (determined by closure of a mechanically-induced wound to a confluent monolayer). HDL (1-30 μg/mL) induced concentration-dependent HUVEC proliferation as well as network formation by HUVEC in Matrigel. The maximal effects of HDL were comparable to those of VEGF. They also depended on the undisturbed function of ATP-dependent potassium channels (K_{ATP} channels) and the activity of endothelial NO synthase (NOS), since treatment with Glibenclamide (a K_{ATP} channel inhibitor, used at 10μM) and L-NAME (a NOs inhibitor, used at 10μM) reduced both effects by more than 80%. We conclude that HDL-induced angiogenic effects on endothelial cells *in vitro*depend on similar mechanisms used by other well-described angiogenic molecules such as VEFG, including NO production and activation of membrane K_{ATP} channels. In ongoing experimental work, we compare the angiogenesis-related effects of HDL from morbidly obese subjects before and after bariatric surgery.

OP14

THE IMPACT OF ESCALATING LOW-DOSE Δ9-THC DURING ADOLESCENCE ON PSYCHOTIC –LIKE SYMPTOMATOLOGY IN ADULT MALE RATS

N. Poulia[1], F. Delis[1], A. Polissidis[2], N. Kokras[3,4], C. Dalla[4], K. Antoniou[1]

[1] Department of Pharmacology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

[2] Laboratory of Neurodegenerative Diseases, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation Academy of Athens, Athens, Greece

[3] First Department of Psychiatry, Eginition Hospital, National and Kapodistrian University of Athens, Athens, Greece

[4] Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Introduction: Preclinical studies suggest that delta-9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive component of cannabis, during adolescence can trigger long-term behavioral/neurobiological alterations and may influence the sensitivity to other "club drugs" or psychostimulants in adulthood.

Aim: Evaluation of behavioral, neurochemical and neurobiological profile in adult rats following adolescent escalating low-dose Δ^9-THC administration.

Methods: Between post-natal day (PND) 35 and 45 adolescent male rats received escalating low-dose Δ^9-THC treatment twice daily (0.3 mg/kg PND35–37; 1 mg/kg PND38–41; 3 mg/kg PND42–45) or vehicle.

During adulthood: a) open-field motor activity was recorded, b) sensorimotor gating was assessed using the Pre-pulse Inhibition test, c) dopaminergic variables were measured in the dorsal striatum, the nucleus accumbens and the prefrontal cortex (PFC), d) dopamine transporter (DAT) protein levels were determined in specific adult brain regions and e) Δ^9-THC-treated rats were injected with an acute d-amphetamine dose (1mg/kg) or saline in adulthood and open-field motor activity was recorded.

Results: a) Δ^9-THC-treated rats showed increased reactivity to novelty versus vehicle. b) Δ^9-THC administration did not influence the filtering of sensorimotor information. c) In the PFC, DA turnover rate was decreased in Δ^9-THC-treated rats, versus vehicle. Decreased striatal dopamine levels and increased DOPAC levels were measured in the nucleus accumbens of Δ^9-THC-treated rats. d) No differences in DAT protein levels were found in both striatal and cortical regions, following Δ^9-THC treatment versus vehicle. e) Adolescent Δ^9-THC pretreatment dampened the motor effects of d-amphetamine during adulthood, as deduced by reduced horizontal-vertical activity, compared with vehicle.

Conclusions: Adolescent low-dose Δ^9-THC administration induced psychomotor stimulation in adult rats, followed by region-specific dopaminergic alterations. No significant deficits in the execution of the pre-pulse inhibition test or changes in DAT protein levels were observed in Δ^9-THC-treated rats. Our results revealed a strong impact of adolescent low-dose Δ^9-THC pretreatment on adult d-amphetamine-induced motor activity. Present findings provide novel information on the consequences of Δ^9-THC treatment during adolescence, while essentially contribute to preclinical/clinical studies focusing on the role of adolescent Δ^9-THC use later in adulthood and its association with the development of psychiatric symptomatology.

OP15

THREE YEARS OF EXPERIENCE FROM USING GAME BASED LEARNING SOFTWARE FOR TEACHING AUTONOMOUS PHARMACOLOGY TO MEDICAL STUDENTS

C. Pourzitaki[1], L. Ioannidis[2], G. Papazisis[1], F. Malliou[1], T. Kirgidis[1], D. Kouvelas[1], P. Bamidis[1]

[1]Laboratory of Clinical Pharmacology, School Of Medicine, Aristotle University of Thessaloniki, Greece

[2]Laboratory of Medical Physics, School Of Medicine, Aristotle University of Thessaloniki, Greece

Purpose: We studied the use and effectiveness of a Game Based Learning software in teaching Autonomous Pharmacology in medical students. We report the results after three years of experience with this teaching method.

Materials and Methods: This randomized, blinded, prospective interventional cohort study, was conducted in the Department of Clinical Pharmacology, Faculty of Medicine, School of Health Sciences, of the Aristotle University of Thessaloniki, from April 2016 to March 2018. One hundred seventy four medical students of the 3rd year participated. Following randomization, the students were divided in control group (N = 92) who attended an educational video lasting 15 minutes and the intervention group (N = 82) who used the Game Based Learning software for the same time period. All students answered a questionnaire of 25 Pharmacology based multiple choice questions. In addition, students from the intervention group answered a questionnaire of 36 questions, which controls the fun and pleasure during the educational process and the motivation for continuing education in order to evaluate the Game Based Learning software. We also compared the grades in the final exams of Pharmacology between the two groups at the end of the spring semester of 2016 and 2017.

Results: Students who used the game had higher grades in the questionnaire compared with students who watched the video ($p < 0,05$). As for the Game Based Learning software the students evaluated positively the interface, its educational value and the commitment of the user playing it. Moreover, the students who used the game achieved higher grades in the final exams ($p<0.01$) while both groups reported that felt motivated to study Pharmacology.

Conclusions: Medical students perform better in understanding and using the concepts of Pharmacology when interacting with Game Based Learning software than when watching an educational video. The use of Game Based Learning software can be an important tool for teaching Pharmacology to medical students in conjunction with traditional training methods.

OP16

EFFECTS OF FOUR HERBAL EXTRACTS ON THE CHARACTERISTICS OF EPILEPTIFORM DISCHARGES IN CA1 PYRAMIDAL CELL LAYER OF RAT HIPPOCAMPAL SLICES

D. Kleidonas[1], A. Troganis[2], H. Stamatis[3], C. Psarropoulou[1]

[1] Laboratory of Animal and Human Physiology, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece

[2] Laboratory of Environmental and Physical Chemistry Studies, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece

[3] Laboratory of Biotechnology, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece

Aim of the study: Recent findings suggest that interictal discharges are related apart from epilepsy to other neurophysiological disorders as well. Here, we investigated the effects of four herbal aqueous extracts on the frequency, amplitude and duration of interictal-like epileptiform discharges (IEDs) of the rat hippocampal CA1 region *in vitro.*

Methods: Aqueous extracts of sage (*Salvia officinalis*), reed (*Acorus calamus*), mate (*Ilex paraguariensis)* and olive tree (*Olea europaea*) were prepared using plant segments. Perfusion of n=71 rat hippocampal slices with Mg^{2+}-free or 50 μM 4-aminopyridine-(4-AP)-containing artificial Cerebrospinal Fluid provoked spontaneous IEDs by activating NMDA receptors or blocking K^+ channels respectively, that were recorded extracellularly before and 10 min after the addition of each extract, in 2 concentrations (C1=1mg/20mL, C2=2mg/20mL) to determine their effects on IED amplitude (1st PS), duration and frequency. Results were statistically evaluated by the Student's t-test (for paired or unpaired samples, as required).

Results: *Acorus calamus* reduced IED amplitude (Mg^{2+}-free: C1 15±6%, n=10, p=0.007; 4-AP: C1 22±5%, n=9, p=0.013) duration (Mg^{2+}-free: C1 12.6±2.9%, n=10, p=0.0005; 4-AP: C1 3.1±0.7%, n=9) and frequency (Mg^{2+}-free: C2 10±3% n=10, p=0.02; 4-AP: C2 3±1%, n=9 p=0.04) in both media independent of concentration. *Salvia officinalis* had similar inhibitory effects in Mg^{2+}-free in a concentration dependent way (n=11), but was ineffective in 4-AP (n=8). *Olea europaea* increased IED amplitude in Mg^{2+}-free (C1 33±15%, n=6, p=0.027; C2 11.5±5.5%, n=6, p=0.031-t) in a concentration dependent way, showing no activity in 4-AP. *Ilex paraguariensis* increased IED frequency (Mg^{2+}-free: C1 17±6%, n=8, p=0.005; 4-AP: C2 12±3%, n=9, p<0.0001), reducing simultaneously IED duration (Mg^{2+}-free: C1 21.5±2.4%, n=8, p<0.0001; 4-AP: C1 2.5±1%, n=9 p=0.0251-t) and amplitude (Mg^{2+}-free C1 12±4%, n=8, p=0.03) in both media and concentration-dependently.

Conclusions: All extracts showed measurable and statistically significant effects in hippocampal IEDs with generally inhibitory (*Acorus calamus, Salvia officinalis*) or excitatory (*Olea europaea, Ilex paraguariensis*) actions. Three of four extracts showed dose-dependent effects, and 2/4 were ineffective in 4-AP suggesting an interference with conductances blocked by 4-AP. Further investigation of the mechanism of action and determination of the active substances within each extract may lead to the development of new drugs with clinical utility.

OP17

EFFECTS OF THE NOVEL DEHYDROEPIANDROSTERONE (DHEA) ANALOGUE BNN27 ON DIFFERENT ANIMAL MODELS OF SCHIZOPHRENIA

E. Zoupa[1], A. Gravanis[2], N. Pitsikas[1]

[1] Department of Pharmacology, School of Medicine, University of Thessaly, Larissa, Greece

[2] Department of Pharmacology, School of Medicine, University of Crete, Heraklion, Greece

Background & Objectives: Consistent experimental evidence suggests the involvement of neurosteroid dehydroepiandrosterone (DHEA) in schizophrenia. BNN27 is a novel DHEA analogue, which devoid of steroidogenic activity and its neurotrophic effect has been observed. Its role, however, in schizophrenia has not yet been established. Thus, the present study was designed to investigate the ability of BNN27 (3, and 6 mg/kg) to counteract schizophrenia-like behavioural deficits produced by ketamine in rats.

Methods: For this purpose, the novel object recognition task (NORT) and the social interaction (SI) test were used. NORT assesses recognition memory, a type of memory impaired in schizophrenics, while SI is an experimental model resembling the negative symptoms of schizophrenia.

Results: Intraperitoneal (i.p.) administration of BNN27 (3 and 6 mg/kg) reversed ketamine (3 mg/kg, i.p.)-induced performance deficits in the NORT. In addition, BNN27 (6 mg/kg, i.p.) seems to attenuate the social isolation caused by ketamine (8 mg/kg, i.p.) in the SI test.

Conclusions: The results of the present preliminary study indicate that BNN27 attenuated schizophrenia-like deficits in animal models resembling cognition deficits and negative symptoms of schizophrenia. The current findings also suggest that further studies should be carried out aiming to elucidate whether or not BNN27 might constitute a potential candidate for the treatment of this psychiatric disorder.

OP18

SYNTHETIC MICRONEUROTROPHIN BNN27 AMELIORATES AMYLOID-BETA PATHOLOGY AND PROMOTES ADULT NEUROGENESIS IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE

K. Karali[1,2], M. Kokkali[1,2], P. Efstathopoulos[2], A. Gravanis[1,2], I. Charalampopoulos[1,2]

[1] *Institute of Molecular Biology and Biotechnology, Foundation of Research and Technology-Hellas (IMBB-FORTH), Heraklion, Greece*

[2] *Department of Pharmacology, School of Medicine, University of Crete, Heraklion, Greece*

Aim: Alzheimer's disease (AD) is characterized by progressive neuronal loss and cognitive decline, while its main neuropathological hallmark is the accumulation of the β-amyloid (Aβ) peptide within the brain. There is now strong evidence that the reduction of neurotrophin Nerve Growth Factor (NGF) is involved in cell death and reduced neurorestoration. BNN27 is a newly developed 17-spiro-steroid analog that mimics the neuroprotective effects of NGF, acting as selective activator of its receptors, TrkA and $p75^{NTR}$ (thus named *microneurotrophin*), promoting neuronal survival. We examined the ability of BNN27 to ameliorate AD-related cognitive decline and neuropathology.

Materials & Methods: BNN27 pellets were sub-dermally applied to 5xFAD mice, which harbor five familial AD mutations, prior to the development of any Aβ pathology (1.5 months of age). The pellets allowed a steady release of the compound over 6 weeks at a concentration of 10mg/kg. Neuropathology and working memory using a T-maze spontaneous alternation test were assessed after treatment.

Results: The 6-week BNN27 treatment significantly improved working memory with the 5xFAD-BNN27 treated animals having significantly better spontaneous alternation performance than the placebo treated. This was paired with decreased Aβ plaque-formation within the dentate gyrus of the hippocampus. Additionally, BNN27 effectively promoted adult hippocampal neurogenesis, significantly increasing the number of doublecortin (DCX) positive neurons, a marker of neuronal precursor cells and immature neurons, within the dentate gyrus of the hippocampus, while partially reduced the accumulation of oligomeric Aβ1-42 in the hippocampus of 5xFAD mice. It is of note that oligomeric Aβ1-42 reduces the proliferation of hippocampal neural stem cells. Furthermore, the integrity of myelin, axons and cholinergic neurons was also investigated. No significant changes of myelin and axonal integrity were observed in the hippocampus after treatment of 5xFAD mice with BNN27. However, BNN27 reduced cholinergic atrophy in basal forebrain of 5xFAD mice, significantly increasing the mean soma size of Choline Acetyltransferase (ChAT) positive neurons.

Conclusions: Our findings suggest that microneurotrophin BNN27 improves cognitive performance, blocks amyloid deposition and promotes hippocampal neuroregeneration in the 5xFAD mice model of AD, most probably affecting the pathways downstream to NGF receptors.

OP19

EFFECTS OF RECEPTOR PROTEIN TYROSINE PHOSPHATASE BETA/ZETA INHIBITORS ON GLIOBLASTOMA CELLS AND ANGIOGENESIS

D. Spyropoulos[1], D. Denekou[1], S. Barmpoutsi[1], M. Drakopoulou[1], P. Castana[1], M. Pastor[2], G. Herradón[2], T. Tselios[3], E. Papadimitriou[1]

[1] Department of Pharmacy, University Of Patras, Patras, Greece

[2] Facultad De Farmacia, Universidad San Pablo-Ceu, Ceu Universities Madrid, Spain

[3] Department of Chemistry, University Of Patras, Patras, Greece

Aim: Receptor Protein Tyrosine Phosphatase beta/zeta (RPTPβ/ζ) is an arising and promising pharmacological target for several pathological conditions, mainly regarding CNS disorders and cancer. RPTPβ/ζ is a transmembrane single-pass protein with a key role on angiogenesis and progress of several types of cancer. In glioblastoma, RPTPβ/ζ is strongly up-regulated and contributes to its highly aggressive phenotype. Therefore, potential inhibition of RPTPβ/ζ suggest an encouraging approach for future treatment of glioblastoma, as well as other cancer types. In the current study, we assessed the biological activity of inhibitors either of the intracellular tyrosine phosphatase domain, or of the interaction of RPTPβ/ζ with its ligands pleiotrophin (PTN) and vascular endothelial growth factor A (VEGF-A) on glioblastoma cell growth and angiogenesis.

Material and Methods: We performed in vitro experiments in two different glioblastoma cell lines, rat glioma C6 and human glioma MO59K cells, and in human umbilical vein endothelial cells. The effect of the tested compounds on angiogenesis in vivo was assessed using the chick embryo chorioallantoic membrane (CAM) assay.

Results: Inhibition of the phosphatase activity of RPTPβ/ζ caused no significant effect on the proliferation or migration of glioblastoma cells and a moderate induction in colony formation in soft agar. No effect on CAM angiogenesis was observed. On the other hand, an inhibitor of the interaction of PTN and VEGF-A with RPTPβ/ζ inhibited the stimulatory effect of PTN and VEGF-A on glioblastoma and endothelial cells, suppressed colony formation of glioblastoma cells and significantly inhibited the in vivo CAM angiogenesis.

Conclusions: The intracellular tyrosine phosphatase activity of RPTPβ/ζ does not seem to play a significant role on the RPTPβ/ζ-mediated effects on glioblastoma cells and angiogenesis. On the other hand, the extracellular domain of RPTPβ/ζ, where both its ligands PTN and VEGF-A bind, seems to play a significant role on both glioblastoma cell growth and angiogenesis and is an interesting target for bioactive molecules development.

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OP20

POTENTIAL ANTICANCER EFFECT OF ANTIPSYCHOTIC DRUGS: IN VITRO INVESTIGATION IN NSCLC CELL LINES

C.E. Andriopoulou, P. Kirgou, P. Pappas, G. Leondaritis, M.Konstandi

Department of Pharmacology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Several epidemiological studies reported significantly lower cancer incidence in male schizophrenic patients compared to general population, although these patients are usually heavy smokers and adopt dietary habits that are largely related to carcinogenicity. The present study investigates the potential anticancer properties of antipsychotic drugs that share a common characteristic- they act as D_2-dopaminergic antagonists. The main focus was on the mechanisms involved in their potential anticancer action on A549 and H1299 non small cell lung cancer lines (NSCLC). For this purpose, the impact of haloperidol, sulpiride, clozapine and risperidone on cancer cell proliferation was evaluated using the SRB test. The NSCLC cells were incubated with the drugs at different concentrations and the drug effect was assessed at different time points. Interestingly, the SRB test and flow cytometry indicated that clozapine markedly reduced the A549 and H1299 cell population by inducing apoptosis, whereas haloperidol and sulpiride, in the concentrations tested that correspond to those used as antipsychotics, had no similar effects. In conclusion, the present findings suggest that several antipsychotic drugs could display anticancer activity. This hypothesis is based on the fact that these drugs reduce the lung cancer cell population by inducing apoptotic mechanisms, and underscores the necessity of further assessing the potential anticancer impact of other antipsychotic drugs, using various cancer cell lines and *in vivo* animal models.

OP21

SIGMA RECEPTORS EXPRESSION IN PANCREATIC CANCER AND EFFICACY EVALUATION OF THEIR LIGANDS USING COMPARE ALGORITHM AND PATIENT DERIVED XENOGRAFTS (PDX)

E. Sereti[1], C. Tsimplouli[1], T. Karagianellou[1], B. Cevatemre[2], E. Ulukaya[3], N. Sakellaridis[1], K. Dimas[1]

[1] Department of Pharmacology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

[2] Department of Biology, Faculty of Arts and Sciences, Uludag University, Bursa, Turkey

[3] Department of Clinical Biochemistry, Faculty of Medicine, Istinye University, Istanbul, Turkey

Aim: Pancreatic cancer is a fatal malignancy, poorly responsive to conventional systemic therapies that result in a progressive resistance to treatment. Sigma receptors (sigma-1 and sigma-2) have recently attracted interest in the field of cancer research and their selective ligands (agonists and antagonists) have been shown to specifically label tumor sites, induce cancer cells to undergo apoptosis and inhibit tumor growth. Aim of this study is to investigate the expression of sigma receptors in pancreatic cancer and their relation to cancer development using Patient Derived Xenografts (PDX), as well as, the efficacy evaluation of sigma receptor ligands as drugs against this type of cancer.

Materials and Methods: Sigma receptors expression was examined using Western Blot. The antiproliferative effect of sigma ligands was studied *in vitro* using the Sulforhodamine B assay and their efficacy was further evaluated using the COMPARE algorithm. The mechanism of action whereby siramesine, a lead sigma-2 agonist, induces cell death and the impact of siramesine on the cell cycle has been investigated using Flow Cytometry and Western Blot. The *in vivo* potency of siramesine, either as single agent or in combination with established drugs, has been studied in patient derived xenograft models of cancer.

Results: Expression of sigma receptors was observed in all examined pancreatic cancer cell lines and tumor tissues. Sigma-2 receptor is highly expressed in cancer compared to adjacent normal tissues and overexpressed compared to sigma-1 receptor. Amongst the sigma ligands tested, siramesine exhibits the best anticancer activity in established cell lines and primary patient derived ex vivo pancreatic cancer cell populations. Furthermore, siramesine induces caspase dependent cell death in a dose and time dependent manner and arrests cells at the $G_{0/1}$ phase. *In vivo*, siramesine exhibits good anticancer activity against a pancreatic cancer PDX and enhances significantly the action of the known chemotherapeutic drug gemcitabine resulting in tumor growth inhibition.

Conclusion: Sigma receptors seem to be a key component for targeting pancreatic cancer and developing novel therapeutic approaches. Sigma-2 receptor agonist, siramesine, shows promising anticancer activity against *ex vivo* pancreatic human cellular populations and in *in vivo* Patient Derived Xenografts of pancreatic cancer.

OP22

EVALUATION OF NOVEL NUCLEOSIDE ANALOGUES FOR LUNG CANCER TREATMENT: AN APPROACH BASED ON METRONOMIC CHEMOTHERAPY

E. Skavatsou, T. Karampelas, C. Tamvakopoulos

Biomedical Research Foundation, Academy of Athens, Center of Clinical Research, Experimental Surgery and Translational Research, Division of Pharmacology-Pharmacotechnology, Athens, Greece

Lung cancer presents a global pandemic responsible for an estimated 20% of cancer cases with Non-Small Cell Lung Cancer (NSCLC) being the most prevalent form. Chemotherapy is the preferred treatment modality for NSCLC, focusing on the disruption of the abnormal proliferation of cancer cells. Nevertheless, this approach causes patients to experience unpleasant side effects resulting in cancer recurrence. Gemcitabine (Gemc) is a nucleoside analogue used against NSCLC, which inhibits the cell cycle and prevents tumor growth. Although gemc is approved for the treatment of various cancer types, its efficacy is limited due to rapid metabolic inactivation. Metronomic chemotherapy (MTR), relying on the daily oral administration of a drug, at low doses, is a multi-targeted therapy, as it inhibits tumor angiogenesis, modulates immunity pathways and effects tumor initiating cells reducing the toxicity of traditional maximal tolerated dose chemotherapy (MTD). Our goal is to provide a new angle in the MTR approach, by examining the efficacy of the daily administration of an oral prodrug of gemc, OralGem, to improve gemc's therapeutic properties.

The A549 lung cancer line was used to establish an *in vitro* model that simulated the MTD versus the MTR conditions. Cells were cultured either in presence of a high concentration of gemc or in medium in which lower concentrations were added daily in order to study alterations in the expression of various angiogenic factors. Additionally, an *in vivo* xenografted animal model was set up to study the effects of MTR chemotherapy on tumor's expansion, angiogenesis and toxicity.

Daily addition of gemc in A549 cells led to a decreased expression of VEGFA, a well-established angiogenic factor, compared to the high dose incubation. In NOD/SCID xenografted mice, the MTR administration of OralGem led to a decreased expression of VEGFA and CD31, a marker found on endothelial cells, suggesting a suppressed angiogenic profile. Finally, MTR administration of Oral Gem led to an increase in the expression levels of Thrombospondin-1, an anti-angiogenic factor, compared to MTD chemotherapy.

MTR administration of OralGem combines restriction of angiogenesis and vessel normalization. Multiple low dosing of OralGem shows improved efficacy compared to MTD administration.

POSTERS SESSION A'

PP1

A NEWLY DEVELOPED DELIVERY SYSTEM FOR VITAMIN D3

M. Rovoli, V. Nikolopoulos, K. Katsoulis, G. Kontopidis

Laboratory of Biochemistry, Veterinary Faculty, University of Thessaly, Karditsa, Greece

Scope: Vitamin D_3 (VD_3) is a liposoluble molecule and its major functions are the increase of intestinal absorption of calcium and promotion of normal bone formation and mineralization (Gueli et al., 2012). VD_3 can also prevent cancer (Saito et al., 2008) and can regulate the immune system (Baeke et al., 2010) and improve insulin sensitivity (Nazarian et al., 2011). However, VD_3exhibits poor solubility.

A new liposome/β-lactoglobulin formulation has been developed as a stable delivery system for VD_3. The aim of this study was the encapsulation of VD_3 into β-lactoglobulin-liposome complexes, recently developed in our laboratory.

Materials and methods: Liposome Preparation:Liposomes encapsulating β-Lg (>90%, Sigma Aldrich) and cholecalciferol (VD_3) (>99%, Sigma Aldrich)were prepared according to the method of (Marsanasco et al., 2011) with some modifications.

Encapsulation Efficiency: Encapsulation efficiency was evaluated by High Performance Liquid Chromatography (HPLC). HPLC provides a convenient method for quantification and characterization of VD_3.

Stability of VD_3 -loaded liposome suspension during storage: Stability was evaluated by turbidity measurements in predetermined time intervals (0 h, 24 h, 48 h and 72 h),

Differential Scanning Calorimetry (DSC) for determination of antioxidant activity: The oxidation activity of samples were evaluated by DSC (Ghatnur et al., 2012).

Results and Discussion: Encapsulation Efficiency: The % EE of VD_3 in liposomes in absence and presence of β-Lg was: 59.42% (± 2.31%) and 96,59% (± 1.52%), respectively.

Stability of VE-loaded liposome suspension during storage: The presence of protein in liposomes formulations of its own also seems to improve system stability..

Differential Scanning Calorimetry (DSC) for determination of antioxidant activity:

The PC/CH/β-Lg/ VD_3 system has a higher oxidation peak (around T_o=335°C) than those of VD_3 (T_o=320°C) and β-Lg (T_o=280°C) in pure forms. It has also the highest oxidation peak of all liposome preparations.

Conclusion: In the present study, we demonstrate that the VD_3 could be efficiently entrapped in liposomes/β-Lg formulation, a newly synthesized promising carrier. Future studies will evaluate the pharmacokinetics and biodistribution of the VD_3/β-LG -loaded liposomes as well as their efficacy to release the vitamin in an appropriate rate.

PP2

A NOVEL UNTARGETED UPLC-HRMS-BASED METABOLOMICS APPROACH IN MICE PLASMA REVEALS SEX DIFFERENCES FOLLOWING I.P. ADMINISTRATION OF TRANS-CROCIN-4

E. Karkoula[1,2], I. V. Dagla[2,3], E. Gikas[3], N. Kokras[1,4], C. Dalla[1], A. L. Skaltsounis[3], A. Tsarbopoulos[1,2]

[1] Medical School, National and Kapodistrian University of Athens, Department of Pharmacology, Athens, Greece

[2] GAIA Research Center, The Goulandris Natural History Museum, Bioanalytical Department, Kifissia, Greece

[3] Department of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece

[4] Medical School, National and Kapodistrian University of Athens, First Department of Psychiatry, Athens, Greece

Aim: *Trans*-crocin 4 (TC4: bis-ester of crocetin with gentiobiose) is the major crocin constituent in saffron stigmas with antioxidant and antiamyloidogenic properties. Metabolomics provides quantitative composition of low molecular weight chemicals in biological systems, providing detailed information on the patterns of metabolite change in an entire metabolic network and also enhances biomarker discovery and interprets the biochemical mechanisms involved in the development and progression of diseases. Although saffron is widely consumed in our diet, there is no study of the alterations in plasma metabolome after TC4 administration. Thus, an untargeted UPLC-High Resolution Mass Spectrometry (HRMS) metabolomics approach has been employed in order to elucidate the mode of pharmacological action of TC4 following its *i.p.* administration to male and female mice.

Materials and Methods: Blood samples from fifty-six mice administered with TC4 including controls were analyzed by UPLC-HRMS (Orbitrap Discovery XL) and were subjected to multivariate analysis (MVA).

Results and Discussion: Statistical evaluation of the results was achieved by (MVA) i.e. principal component analysis (PCA), Partial-Least Squares–Discriminant Analysis (PLS–DA) in order to discover the features contributing to the discrimination between treated and untreated groups. These variables were further identified using comparisons to online databases (e.g., Metlin, HMDB) along with software manipulations, e.g., adduct and fragment identification. A multilevel PLS-DA splitting variation to each individual component has proven to be a more suitable approach due to the high variability imposed by various factors (sex, administration dose and time-points of sacrifice). A preliminary sex-related effect on the metabolome has been proven to exist, denoting that the administration in both genders is indispensable in order to acquire safe conclusions as reliable metabolome pictures.

Conclusions : *I.p.* administration of TC4 proved capable of causing alterations to the metabolic profiles of the mice. Furthermore, a ML-MVA approach revealed internal differences among the treated populations, which are related to either their sex or the time-point of the sacrifice. Finally, subsequent metabolic pathway analysis of the annotated metabolites revealed that the steroid hormone biosynthesis has been mostly influenced.

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PP3

AN ASSOCIATION STUDY OF PNPLA3 I148M WITH LIPIDEMIC AND GLYCEMIC MARKERS AND TYPE 2 DIABETES IN HYPERLIPIDEMIC PATIENTS

D. Ioannidou[1], A. Goulas[1], G. Germanidis[2], D. Agapakis[3], C. Savopoulos[3], A. Hatzitolios[3]

[1] 1st Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] 1st Department of Internal Medicine, AHEPA Hospital, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[3] 1st Propedeutic Department of Internal Medicine, AHEPA Hospital, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

Introduction-Aim: The *PNPLA3* I148M polymorphism (rs738409), in the gene coding for patatin-like phospholipase 3 has been repetitively associated with pathogenesis and development of non-alcoholic fatty liver disease (NAFLD). PNPLA3 displays monoacyl-, diacyl-, and triacylglycerol hydrolase activity (decreased as a result of the I148M substitution), as well as lysophosphatidic acid acyltransferase activity (increased as a result of the I148M substitution), is actively involved in hepatocyte triacylglycerol metabolism, and may also related to systemic homeostasis of glucose. Despite NAFLD being intimately connected to dyslipidemia, insulin resistance and hyperglycemia, no association of rs738409 with lipidemic and glycemic indices has been established thus far. In this study we examine the association of rs738409 with blood serum triacylglycerol (TG) and total cholesterol (TC) levels, and with glycated hemoglobin (HbA1c) in a group of previously examined hyperlipidemic patients from northern Greece.

Materials and Methods: One hundred and sixty-five newly diagnosed, treatment-naove, hyperlipidemic patients participated in this study. Patients had been diagnosed in the outpatient clinic of the 1st Propedeutic Department of Internal Medicine at AHEPA University Hospital, Thessaloniki, and in the lipid outpatient clinic of Goumenissa General Hospital (Kilkis prefecture), from 2009 till 2012. Serum TC and TG concentrations were determined with standard biochemical procedures. HbA1c was determined with an HPLC-based method. Genotyping of the rs738409 polymorphism was based on a previously reported PCR-RFLP method. The association of the polymorphism with serum parameters was tested with ANCOVA in the entire sample and following stratification according to obesity and type 2 diabetes (T2D) diagnosis. Genotype distributions were compared between different subgroups with the x^2 test of independence.

Results: No association of rs738409 with serum TG, TC or HbA1c was detected, in the total sample or in the stratified subgroups. An ostensibly protective action of the minor allele (G, 148M) with respect to T2D was observed however.

Conclusion: Our results are in agreement with previously reported associations of rs738409 with increased insulin sensitivity and implications of a systemically benign effect.

PP4

ANTIFUNGAL ACTIVITY OF PISTACIA LENTISCUS L. GROWING IN THE ISLAND OF CHIOS-GREECE AGAINST MALASSEZIA SPS

A. Velegraki[1], K. Graikou[2], C. G. Ganos[2], E. Smyrnioudis[3], I. Chinou[2]

[1] Division of Microbiology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[2] Division of Pharmacognosy & Chemistry of Natural Products, Faculty of Pharmacy, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[3] Chios Mastic Growers Association, Kardamada, Chios, Greece

Objectives: In the framework of our investigations on the bioactivities of natural products, we report in this study the activities of selected extracts and the oil from Mastix resin,, against *Malassezia* yeasts. Mastix is a well-known natural resin from the trunk and branches of*Pistacia lentiscus* L. (Anacardiaceae), which is grown as cultivar widely in the Greek island of Chios. It has been mentioned by famous ancient Greek physicians (Dioscorides, Theophrastos etc) for its healing properties, while it has been used in traditional Greek medicine for various gastrointestinal disorders as well as skin inflammations. These indications of the resin have been recently approved by European Medicines Agency (EMA) too.

Method: *Malassezia* yeasts are members of the normal human skin ?ora, associated with a number of dermatological disorders (including dandruff/seborrheic dermatitis and pityriasis versicolor) and systemic infections in subgroups of severely immunocompromised patients. The pure natural resin (mastixc together with its essential oil and two fractions of the resin (neutral and acidic) were studied for their activities against a panel of *Malassezia* sps. A total of 18 type, reference and clinical *Malassezia* strains (*M. furfur*, *M. restricta* and *M. globosa*) were tested in vitro.

Results: The pure natural resin and its acid fraction showed bio-activity against the major dandruff agents at clinically significant concentrations (MIC 2-64mg/L) comparable to the activity of the known antibiotic amphotericin B, while the neutral fraction (MIC 128-512mg/L) demonstrated limited activity and the mastic oil no activity against *Malassezia* clinical strains.

Conclusions: The results of this study signify the prospects that mastic resin may have interesting applications to control *Malassezia*fungal-derived disease and potentially lead to the development of herbal formulation against infections caused by *M. furfur*.

PP5

ANTIPLATELET EFFECTS OF NILOTINIB AND SYNTHETIC ANALOGS, IN VITRO

D. Pantazi[1], N. Demou[2], K. Skobridis[2], A. D. Tselepis[1]

[1] Atherothrombosis Research Centre, Laboratory of Biochemistry, Department of Chemistry, University of Ioannina, Ioannina, Greece

[2] Laboratory of Organic Chemistry, Department of Chemistry, University of Ioannina, Ioannina, Greece

Background: Tyrosine kinase inhibitors (TKIs) such as nilotinib is an important drug for the treatment of Chronic Myeloid Leukemia (CML). Except of this activity nilotinib may influence the functionality of other cell types including platelets. Moreover, this TKIs can increase the risk for heart/vascular implications leading to the production of pathological thrombus.

Aim of the study: To explore the possible antiplatelet effects of nilotinib and four structurally related synthetic analogs in human platelets, *in vitro*.

Methods: We designed and synthesized four nilotinib analogs named as SK20, C24, AG18, AG20 following the classical synthetic methods of pyrimidine ring systems. Each analog as well as nilotinib were studied for their possible antiplatelet effects on platelet aggregation in platelet rich plasma (PRP) induced by the platelet agonists adenosine diphosphate (ADP, 5 μM), thrombin receptor activating peptide-6 (TRAP-6, 10 μM) and arachidonic acid (AA, 500 μM).

Results: Each synthetic substance was characterized by spectrometric methods (IR, HRMS & NMR). Nilotinib inhibited platelet aggregation was induced only by AA (500 μM), exhibited an IC_{50} value of 3.9 μM.

All the synthetic analogs studied inhibited platelet aggregation induced by AA. Importantly compounds SK20, AG18 and AG20 were less potent compared with nilotinib whereas the compound C24 exhibited a 10-fold more potent antiplatelet activity (IC_{50}=0.4 μM) compared with nilotinib. Furthermore it should be stated that in contrast to nilotinib and the other analogs compound C24 also inhibited platelet aggregation induced by ADP and TRAP-6 showing IC_{50} values 24.8 and 15.5 μMrespectively.

Conclusions*:* By reversing the amide bond and replacing the imidazole ring by nitro- and chloro- group in nilotinib, the synthetic compound exhibits a more potent antiplatelet activity than nilotinib. The importance of this finding needs further investigation.

PP6

BEHAVIOR OF EGG-YOLK POLYPHOSPHOPROTEINS TOWARDS REDOX-ACTIVE METAL-INDUCED OXIDATION OF BIOLOGICAL MACROMOLECULES IN VITRO

K. Siatra[1], A. Palaiologou[1], K. Makedou[2], A. Goulas[1]

[1] 1st Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] Laboratory of Biological Chemistry, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

Introduction-Aim: Phosvitins (PVs) are polyphosphoproteins stored in the egg yolk of most oviparous animals. By virtue of their long stretches of phosphorylated serine residues, PVs display excellent metal-chelating properties; they can bind iron with high affinity, but also copper, calcium, magnesium, manganese, cobalt and even uranium. This metal-binding activity can disrupt redox cycling between different oxidation states of bound ions, thus endowing PVs with some potentially useful antioxidant properties. On the other hand, redox-active metal binding can also work in a pro-oxidant fashion, as in the case of many antimicrobial peptides and other metal-binding antibiotics. In this study we examine the effect of various preparations of chicken (*Gallus gallus*) and trout (*Oncorhynchus mykiss*) PV, on the oxidative damage of DNA and serum lipoproteins affected by iron and copper ions.

Materials and Methods: Isolated PVs of high purity, practically free of copper or iron, were used in this study. The effect of PVs on the copper-induced oxidation of serum lipoproteins was assayed with a previously reported method. Copper- and iron-induced ϕ phage DNA degradation was assayed with an in-house developed system based on a previously published method.

Results: PVs were able to protect ϕ phage DNA from redox-active metal-induced degradation. Efficacy was higher towards iron than it was towards copper ions, with the major chicken sub-fraction (Clark1) affording the best protection from degradation. Phosvitin preparations did not display anti-oxidative behavior in the serum lipoprotein oxidation assay however, and they even acted as pro-oxidants at certain Cu^{2+}: PV ratios.

Conclusions: Phosvitins from chicken and trout and their sub-fractions can protect DNA from redox-active metal-induced degradation but can also function as pro-oxidant agents at certain conditions.

PP7

BNN27 EXERTS SIGNIFICANT EFFECTS ON HUMAN FIBROBLASTS DURING WOUND HEALING IN VITRO

I. Axiotis[1], K. Kalligianni-Sofikiti[1], G. Sakellaris[2], M. Venihaki[1]

[1] Department of Clinical Chemistry, Faculty of Medicine, School of Health Sciences, University of Crete, Heraklion, Crete, Greece

[2] Department of Pediatric Surgery, University Hospital of Heraklion, Heraklion, Crete, Greece

Aim of the study: Cutaneous wound healing is a complex process, which requires the cooperation of many different cell populations and factors. Several studies have suggested that the nervous system is involved in the process of healing through neuropeptides and neurosteroids produced and/or released locally. Dehydroepiandrosterone (DHEA) is a ubiquitous adrenal and neurosteroid hormone with strong neuroprotective and immunomodulatory properties. Its synthetic analogue, BNN27 (now called microneurotrophin), which cannot be converted to estrogen or androgen, seems to conserve these properties when used in an in vivo animal model of inflammatory pain and LPS-induced brain inflammation. We have shown previously that treatment with BNN27 decelerates cutaneous wound healing in vivo. Based on the above, the aim of the present study was to investigate the effects of BNN27 on wound healing in vitro and to further understand the mechanisms mediating these effects.

Methods: For our studies we used primary fibroblasts isolated from explants of foreskin obtained at the time of circumcision for unrelated problems. Fibroblasts were initially cultured with DMEM/10% FBS and the day of the experiment the media were replaced with fresh media containing vehicle or BNN27 at 10^{-8} M. The proliferation rate of the cells was evaluated over a four-days period with the MTT method. The migration rate was examined with the scratch assay and the contraction rate was tested with the gel contraction assay.

Results: Human fibroblasts, when they were treated in vitro with BNN27 (10nM) had significantly increased proliferation rate at 24 hours. Similarly, the same concentration significantly increased the contraction rate of the cells, while no effect was observed in the migration of the cells. Finally, BNN27 at the same concentration significantly increased IL-6 protein levels at 12 hours.

Conclusions: Our data demonstrate considerable effects of BNN27 on wound healing in vitro and may help in the development of new therapeutic regimens for treating abnormal healing and related diseases.

PP8

BORAGINACEAE PLANT FAMILY, AS SOURCE OF BIOACTIVE METABOLITES. ANTIMICROBIAL, ANTIPLASMODIAL, LEISHMANICIDAL AND ANTIPROLIFERATIVE ACTIVITIES

K. Graikou[1], K. Sykłowska - Baranek[2], H. Damianakos[1], C. Ganos[1], P. Le Pape[3], C. Roussakis[4], A. Pietrosiuk[2], I. Chinou[1]

[1] Division of Pharmacognosy & Chemistry of Natural Products, Faculty of Pharmacy, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[2] Department of Biology and Pharmacy Botany, Faculty of Pharmacy, Warsaw Medical University, Warsaw, Poland

[3] Lab de Parasitologie et Mycologie mıdicale, BioCiT, Universitı de Nantes, Nantes, France

[4] Department de Biologie Cellulaire, Facultı de Pharmacie, Universitı de Nantes, Nantes, France

Objectives: Boraginaceae is a family of herbs, widespread (approx. 2300 species), in Mediterranean Europe and Asia. Species of the familyare investigated for the presence of pharmacologically active/toxic compounds, among which the most significant are: red naphthoquinones, other phenolics and pyrrolizidine alkaloids. In the framework of our research on the Boraginaceae family, we report herein a selection of interesting bioactivities among selected Greek species (*Rindera graeca*, *Onosma graeca, O. rigida, O. erecta, Alkannacorcyrensis, A. sfikasiana, Arnebia euchroma)* from nature and *in vitro* cultures (*R graeca*, *A euchroma*).

Methods: Qualitative phytochemical investigation of all above plants resulted to the isolation of A). 9 isohexenylnaphthazarins of alkannin and shikonin structures from *n*-hexane extracts B). several flavonoid and caffeic acid derivatives (luteolin, apigenin, quercetin and kaempferol di and tri glucosides and caffeic acid derivatives such as rosmarinic, lithospermic and rabdosiin respectively) and C). pyrrolizidine alkaloids and N-oxides. All structures were determined by modern spectral means (LC-MS, and NMR).

Their *in vitro* antimicrobial activities were determined, by measuring their MICs against a panel of 6 bacteria (Gram±) and three fungi, pathogenic for humans. All naphtazarines have been also tested *in vitro* against *Leishmania mexicana* and *in vivo* against *Plasmodium berghei Anka* using the Peter's test for 21 days in three groups of 7 Swiss mice each. Moreover, they have been assayed for their antiproliferative activities against two lung cancer cell lines (NSCLC-N6 and A549) of human origin.

Results: Through the antimicrobial screening, the extracts and red naphtazarines showed a very interesting antimicrobial profile, while it is noteworthy that acetylshikonin was active against *Leishmaniam mexicana (*CI50 0.385 +/- 0.02 μg/ml) and *Plasmodium berghei.* One red pigment showed an interesting antiproliferative dose-dependent cytostatic activity against NSCLC-N6.

Conclusions: The results of the assays revealed that naphtazarines, possess strong antimicrobial activities against all tested microbia and parasites, while through *in vivo* test, did not show any toxicity. The antiproliferative activities of one among red pigment, is still in progress, while the preliminary results are very promising to its influence to the expression of selected genes.

PP9

CLONING AND EXPRESSION OF RECOMBINANT HUMAN A-GLOBIN THROUGH PTD TECHNOLOGY: STUDY OF ITS INTRACELLULAR TRANSDUCTION IN K562 PROERYTHROID CELL CULTURE

A. Miliotou, D. G. Laspa, L. C. Papadopoulou

Laboratory of Pharmacology, Faculty of Pharmacy, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

Purpose – Introduction: Combinational cloning technology complemented by the Protein Transduction Domain Technology (PTD) was applied to attempt targeted intracellular delivery of recombinant fusion α-globin in eukaryotic cells. Protein transduction technology uses small peptides, called PTDs (Protein transduction Domains) or CPPs (Cell Penetrating Peptides) to penetrate almost all biological membranes, accumulating intracellularly with their therapeutic cargos. Congenital hemoglobinopathies, like α- and β- thalassemias, are a diverse class of human genetic disorders that are prevalent in the Mediterranean and result in the absence or reduced levels of functional hemoglobins in red blood cells.

Material-Methods: In this study, we have designed and carried out the cloning of the α-globin CDS fused to the nucleotide sequence of the TAT peptide and the epitope HA in both pCRII-TOPO vector and the bacterial expression vector pET-16b. In addition, we cloned the human α-globin CDS, fused to the nucleotide sequence of the HA epitope. Next, we produced the corresponding recombinant fusion proteins, 10xHis-XaSITE-TAT-α-globin-HA and 10xHis-XaSITE-α-globin-HA, to be used as a negative control in the intracellular transduction experiments, after transformation of freshly produced competent bacterial E. coli cells. Results Produced proteins were harvested from IPTG-induced bacteria in the form of inclusion bodies (IBs) and solubilized in 1M L-Arginine solution. We then purified the corresponding soluble recombinant proteins by affinity Ni2+-NTA chromatography under denaturing conditions. The recombinant His-tagged fused a-globin proteins were eluted from the column by adding gradient imidazole concertation buffers. 10xHis-XaSITE-TAT-α-globin-HA and 10xHis-XaSITE-α-globin-HA proteins were characterized by Western Blot analysis with both anti-His antibody as well as anti-Hemoglobin α.IgG antibody. Additional experiments are underway to demonstrate the transduction of recombinant fused human TAT-α-globin-HA in cultured K-562 cells.

Conclusions: Our results indicated that the human recombinant TAT-α-globin fused variants can be produced in bacteria. Successful transduction of TAT-α-globin into eukaryotic cells as expected will allow our group to further study its functionality.

PP10

CORRELATION BETWEEN TESTOSTERONE AND BIORRYTHMIC PROFILE

K. Dimoulas, T. Papadimitriou, E. Dimoulas, E. Velliou, A. Galli, K. Teliou, A. Oikonomou, I. C. Drossinou, K. Zambakas, I. Seidou, D. Liovas

Psychobioanalytical Research Working Group "ἐκ τῶν ὑστέρων"

Our goal was to see, bibliographically, whether drugs containing testosterone could act, positively or negatively, on the patient receiving them, calculating their (regular or emergency) intake during function of the biorhythms, which, as the science of chronobiology, is a great chapter of, at least, that we know of so far, Phychiatry. In particular, we will see the correlation between testosterone and monthly biorhythms of both physical and emotional, first by revising the beginning of their calculation, from the date of birth to that of the conception, and secondly of their characterization as male and female in male and female respectively. At least from the science of neuropsychology, we are now in a position to reliably measure the function of the biorhythms far behind the date (previously in the 5th and already in the 3rd month of pregnancy) that Legal Science considers the embryo as a being of law, reaching, with gynecological calculations at zero point (conception). From that moment, the genital system enters a race for expression, after the third month, of genotype sex and phenotypically. The, by sex, expression of genital biological factors (chromosomal mosaic) through sex hormones in a mix reaches 43,046,721 combinations, which can be roughly summed in 81 combinations,superficially, only, differentiated in the two sexes. There are not two sexes, but the "human" that happens to perform functions that, by sex, move on to a continuous, the two ends of which occupy the (theoretically) totally male and the (theoretically) perfectly feminine, between of which there is the mixing of (more) the male to the female and (less) the female to the male. Distinction "man - woman" must be replaced by the continuous "male - female". Thus, body biorhythm, as a "male", is biorhythm and of women, emotional biorhythm, as "female", is biorhythm and of men, in principle. First biorhythm is 23 days and the second 28, with the rising and falling, centered on the zero base line, peaked in the first and third quarters of each. This is case, by time of conception and should be taken into account by the sponsor of drugs containing testosterone.

PP11

CORRELATION BETWEEN THE CNS GENES OPRM1 (RS1799971), DRD2 (RS1800497), BDNF (RS6265) AND NICOTINE ADDICTION IN A SOUTH EASTERN EUROPEAN POPULATION

K. Sarantidis, S. Nioma, E. Kokkiou, M. S. Katsarou, M. Lagiou, T. Kalogridis, N. Drakoulis

Research group of Clinical Pharmacology and Pharmacogenetics, Faculty of Pharmacy, School of Health, National and Kapodistrian University of Athens, Athens, Greece

Nicotine is highly addictive. Entering the body, it binds to nicotine receptors (nAchRs) in CNS and regulates the release of neurotransmitters such as dopamine and β-endorphin. The *OPRM1* gene encodes the mu opioid receptor, which is a target for β-endorphin. The *DRD2* encodes the D2 receptor of dopamine. The *BDNF* gene encodes the protein neurotrophin, which plays a role in dopaminergic and GABA-ergic neurons' development and survival. The purpose of this study is to investigate the polymorphisms rs1799971 *(OPRM1),* rs1800497 (*DRD2*) and rs6265 *(BDNF*) in association with nicotine addiction, as these specific genes play an indirect role in the pathway of nicotine inside the human body.

DNA samples have been collected in buccal swabs from 314 volunteers (South Eastern Caucasians, SEC), who were then divided in two groups: smokers (109) and non-smokers (205). Genotyping was performed with real-time PCR (LightCycler 480, Roche) and appropriate LightSnip Assays (TIBMOLBIOL). All samples were anonymized and randomized after the volunteers signed an inform consent.

Among smokers, rs1799971 A:A genotype appears 34% more frequent than mutant genotypes,rs1800497 C allele appears 23% more frequent, while the rs6265 A:A mutant genotype is 3 times more frequent than the wild type.

These observations agree to previous studies that indicate rs1799971 A:A genotype, rs1800497 C allele and rs6265 A:A genotype to be linked with higher reward feeling while smoking and lower abstinence periods of smoking cessation. It seems there is a relation between the polymorphisms and nicotine addiction, but further investigation to larger populations is needed to have statistically significant results.

PP12

CORRELATION TESTOSTERONE AND BIOSEXHORMONIC PROFILE

K. Dimoulas, T. Papadimitriou, E. Dimoulas, E. Velliou[1], A. Galli, K. Teliou, A. Economou, I. C. Drosinou, K. Zambakas, I. Seidou, D. Liovas

Psychobioanalytical Research Working Group "ἐκ τῶν ὑστέρων"

Our goal was to put the established association of testosterone with aggression in a new perspective, that of correlation of aggression not with phenotypic but with genotypic sex, in the sense of the exact point in the biopharmaceutical continuum in which the individual is found, that takes drugs with testosterone. Studying the individual biosexhormonic differences, computing the many, even within the group of men and women, deviations, we proceeded (descriptive / statistical / interpretive method), working on the findings of Magnus Hirschfeld on biopharmomorphic behavior. The separation of the individuals, that we did, was according to the physical (from hormones) characters [primary (genital parts: seminal epithelium, pores, genital udder, genital slit), secondary (chest / breast, hair, carotid / voice, pelvis, skeleton/muscles)], the sexual (sexhormonic expression) instinct (tedency, approach, sensations, energy) and the [after effect of the chromo-communication of our chromosomal background (of our genome in particular) and of the brain] behavior (emotional life, emotions, mental skills, employment, dressing) of people. We found that, the by gender (the expression of genital biological factors (chromosomal mosaic), through sex hormones, in a mix), behavior reaches (according to the mixed, psychosomatic, characteristic features of the individual) the 43.046.721 types, who are roughly summed in 81 combinations, superficially, only, differentiating in both sexes. Research findings confirm the importance of genital biological factors (chromosomal mosaic), expressed through sex hormones, mixed. Of course, there are not two sexes, but the "human" happening to perform functions that, by sex, move in a continuous, the ends of which occupy the (theoretically) totally male and the (theoretically) perfectly feminine, between of which there's the mixing of (more) the male to the female and (less) the female to the male. So, the apparent separation of people into two sexes very little corresponds to reality, as dictated by the biopsychological substrate of each. The distinction "man - woman" must be replaced by the continuous "male - female". Anyway, only the knowledge of which point of the gender continuum is the human can help us to better interpret the expression of genotypically dictated, by testosterone, aggressiveness, increased by drugs with testosterone.

PP13

CRITICAL ROLE OF SEX STEROID HORMONES IN THE REGULATION OF HEPATIC CYP2D IN FEMALE WILD TYPE AND HUMANIZED MOUSE MODELS

M. Konstandi[1], C. E. Andriopoulou[1], J. Cheng[2], F. J. Gonzalez[2]

[1] Laboratory of Pharmacology, Medical School, University of Ioannina, Ioannina, Greece

[2] National Institutes Of Health, National Cancer Institute, Greece

Cytochrome CYP2D is expressed in various tissues including liver, intestine, kidney and brain and catalyse the hepatic metabolism of about 25% of the prescribed drugs including the vast majority of antidepressants, antipsychotics, antiarrythmics and anticancer drugs. At present, our knowledge about CYP2D regulation remains largely blared. The present study investigated the role of sex steroid hormones in the regulation of CYP2D in the liver. The hepatic *Cyp2d22* expression was assessed in the distinct phases of the estrous cycle of normo cyclic C57BL/6J (WT) and CYP2D6-humanised (hCYP2D6) female mice. The hepatic expression of *Cyp2d22* was also evaluated in ovariectomized mice of both strains and comparisons were made to male mice. Ovariectomised mice were also supplemented with 17β-estradiol (E2) and/or progesterone (P). In order to further elucidate the role of estrogens in CYP2D regulation, tamoxifen was administered in intact cyclic females. The data of this study revealed that hepatic *Cyp2d22* mRNA and protein levels were higher at estrous compared to the other phases of the estrus cycle and ovariectomy repressed *Cyp2d22* expression in WT mice. Estradiol and/or progesterone prevented the ovariectomy-mediated *Cyp2d22* repression via activation of PI3k/Akt signaling pathway. These alterations were highly correlated with those in HNF1a mRNA expression. In contrast, ovariectomy markedly induced *CYP2D6* expression in the liver of hCYP2D6 mice, a fact that was reversed by hormonal replacement therapy using E2 and/or P. Finally, tamoxifen suppressed the *Cyp2D* expression via PI3k/Akt and MAPK (ERK and p-38) signaling pathways in WT female mice. Apparently, sex steroid hormones display a significant gender- and species-specific role in the regulation of hepatic CYP2D.

PP14

DEGLUCOHELLEBRIN: A NOVEL PLANT-DERIVED COMPOUND FOR GLIOBLASTOMA TREATMENT

E. Vartholomatos[1], G. Alexiou[1], G. Markopoulos[2], D. Lazari[3], O. Tsiftsoglou[3], I. Chousidis[4], I. Leonardos[4], A. P. Kyritsis[1]

[1] Neurosurgical Institute, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

[2] Laboratory of Biology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece & Division of Biomedical Research, IMBB-FORTH University Campus, Ioannina, Greece

[3] Laboratory of Pharmacognosy, Division of Pharmacognosy- Pharmacology, Faculty of Pharmacy, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[4] Zoology Laboratory, Department of Biological Application and Technology, School of Health Sciences, University of Ioannina, Ioannina, Greece

Objective: Glioblastoma, a WHO grade IV glioma, is the most common primary brain tumor in adults with a medium survival of 15 months. This difficult to treat tumor is very heterogenous with evident pathological and genomic variants. Furthermore, the presence of the physiological blood–brain barrier (BBB) creates a pharmacological sanctuary. Thus, it is of paramount importance the development of agents with low molecular weight that can readily cross intact BBB. To date several anticancer agents have been isolated from plants. *Helleborus odorus* subsp. *Cyclophyllus* is an endemic plant of the Balcan flora. The present study investigated for the first time the effect of deglucohellebrin (DGH) extracted from roots of *Helleborus* in glioblastoma.

Materials-Methods: We investigated the effect of DGH in 3 glioblastoma cell lines (U251MG, T98G and U87G). We selected the T98G cells because of their inherent temozolomide resistance, the major chemotherapeutic agent for glioblastoma treatment. Viability assay, flow cytometric analysis of DNA cell cycle, Caspase-8 activity, Mitochondrial membrane potential (ΔΨn) and CD24/CD44/CD26/CD28/CD38/CD62-L/CD15/CD56/CD58/CD71/CD122 analysis was performed. Acute Toxicity tests, morphological observations and behavioral analysis were performed in Zebrafish models.

Results: The IC_{50} values of DGH was 7μM in U251MG cell line, 4μM in U87G cell line and 5μM for the temozolomide resistant T98G cell line. DGH produced G2/M cell cycle arrest, caspace-8 activation and significant mitochondrial membrane depolarization suggesting activation of the intrinsic (mitochondrial) apoptotic pathway. We then compared DGH with temozolomide for the induction of CDs expression in two cell lines (U251MG and T98G) and we found significant changes in CD24/CD26/CD38/CD44/CD62-L/CD15/CD56 and CD122 expression. In zebrafish, DGH did not induce toxicity or behavioral alterations even at a concentration of 1mM.

Conclusions: The present study is the first to determine the effect of DGH in glioblastoma. We found that DGH has a sustained antiproliferation activity in glioma cell lines at very low concentrations and induces apoptosis. More importantly DGH did not induce toxicity and had no effect on behavior in zebrafish. DGH may be a promising new plant-derived compound for glioblastoma treatment.

PP15

DIETARY SUPPLEMENTATION IN MULTIPLE SCLEROSIS

C. Tryfonos[1], C. Giaginis[1], D.Fotiou[2], M.Vrizas[3], K. Vadicolias[4]

[1] University Of The Aegean, Myrina, Lemnos, Greece

[2] School Of Medicine, Aristotelian University Of Thessaloniki, Thessaloniki, Greece

[3] School Of Medicine, Democritus University Of Thrace, Alexandroupoli, Greece

[4] Democritus University Of Thrace, Medical School, Alexandroupoli, Greece

Aim: This study aims to critically summarize and evaluate the currently available clinical studies, focusing on the potential beneficial effects of dietary supplements on controlling multiple sclerosis (MS) symptomatology and relapse.

Materials/Methods: PubMed database was comprehensively searched by the use of various relative keywords in order to identify clinical trials investigating the potential beneficial effects of dietary supplementation for controlling MS.

Results: Nutritional status and dietary supplementation has been suggested as potential factors affecting both disease risk and progression in the course of multiple sclerosis with complex genetic-risk profiles. Several substantial studies have documented low plasma vitamin A, B12 and D_3 levels in patients suffering from MS. Some dietary supplements seem to exert antioxidant properties, improving quality of life in MS patients. Nutritional status has not adequately been examined in order for at least indicative evidence to be drawn.

Conclusions: According to the existing clinical studies, some dietary supplementation may decrease inflammation, fatigue and improve quality of life, while some others may increase autoimmunity tolerance in MS patients. However, it must clearly be stated that, at the present time, there is no clear clinical indication for using dietary supplementation as a treatment for MS. Further clinical trials in each dietary supplementation separately as a potential co-treatment agent or as an add-on option are strongly recommended.

PP16

DISTRIBUTION OF THE LPLS447X POLYMORPHISM IN CHRONIC HCV PATIENTS AND CONTROLS

A. Goulas[1], A. Palaiologou[1], A. Apostolidis[1], V. Sevastianos[2], J. Koskinas[3], G. Papatheodoridis[4], T. Vasiliadis[5], E. Sinakos[6], D. Agapakis[7], G. Germanidis[8]

[1] 1st Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] Department of Internal Medicine, Evangelismos General Hospital of Athens, Athens, Greece

[3] 2nd Academic Department of Internal Medicine, Hippokration Hospital of Athens, Athens, Greece

[4] Department of Gastroenterology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Laikon General Hospital of Athens, Athens, Greece

[5] 3rd Department of Internal Medicine, Papageorgiou Hospital of Thessaloniki, Aristotle University of Thessaloniki, Thessaloniki, Greece

[6] 4th Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Hippokration General Hospital of Thessaloniki, Thessaloniki, Greece

[7] 1st Propedeutic Department of Internal Medicine, AHEPA Hospital of Thessaloniki, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[8] 1st Department of Internal Medicine, AHEPA Hospital of Thessaloniki, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

Introduction-Aim: Lipoprotein lipase is a key enzyme in lipid metabolism, catalyzing the hydrolysis of triglycerides in chylomicrons and very low density lipoprotein (VLDL) remnants. Over the last few years LPL was identified as an anti-hepatitis C virus (HCV) host factor, in view of its ability to inhibit HCV infection of hepatoma cells in culture and in primary human hepatocytes transplanted into mice. Both the catalytic and the structural (bridging) function of LPL have been implicated in this process. *LPL* S447X (rs328) is a common polymorphism produced from a nonsense mutation which removes the last two C-terminal amino acids and confers increased lipolytic activity to the enzyme. The aim of our study was to compare the distribution of rs328 in chronic HCV patients and in control individuals displaying no signs/symptoms of chronic HCV infection.

Materials and Methods: We have genotyped the rs328 polymorphism in the DNA of 161 previously characterized patients with chronic HCV infection and of 147 controls, with an established PCR-RFLP method. A group of previously characterized hyperlipidemic patients (n = 163) was also included in the comparison. The rs328 genotype frequencies were compared between infected patients and controls with the x^2 test of independence. The association between rs328 and plasma lipid parameters of a subset of chronic HCV patients at baseline was examined with ANCOVA.

Results: No statistically significant difference was detected in the rs328 genotype frequencies between chronic HCV patients, controls or hyperlipidemic patients. No association between plasma lipids of chronic HCV patients and the rs328 polymorphism was detected either.

Conclusions: Carriage of the gain-of-function rs328 G allele (*LPL* 447X) does not appear to afford protection from chronic HCV infection, in spite of LPL having been characterized an anti-HCV host factor.

PP17

EFFECT OF SACUBITRIL/VALSARTAN ON CIRCULATING CATECHOLAMINE LEVELS DURING A 6 MONTH FOLLOW UP IN STABLE HEART FAILURE PATIENTS. TIMEO DANAOS ET DONA FERENTES?

G. Chalikias[1], P. Kikas[1], P. Rigopoulos[1], A. Pistola[2], A. Zisimopoulos[2], D. Tziakas[1]

[1]Cardiology Department, Medical School, Democritus University of Thrace, Alexandroupolis, Greece

[2]Nuclear Medicine Department, Medical School, Democritus University of Thrace, Alexandroupolis, Greece

Background: Recently, the PARADIGM-HF trial demonstrated the superiority of Sacubitril/Valsartan over enalapril on the composite of death from cardiovascular causes or hospitalization for heart failure (HF). With the present study assessed the effect of Sacubitril/Valsartan on circulating catecholamine levels in patients with HF in an observational cohort study.

Methods: We included 54 consecutive HF patients attending our HF Outpatients Clinic who were eligible to Sacubitril/Valsartan according to the PARADIGM-HF inclusion and exclusion criteria. Norepinephrine and epinephrine were measured with immunoradiometric assays at baseline, at 3- and at 6-month time follow-up.

Results: Compared to baseline levels there was no change at three months in epinephrine (P=0.177) or norepinephrine (P=0.815) concentrations. At 6 months norepinephrine remained unchanged (P=0.359). However, at 6 months we observed a significant increase in epinephrine levels compared to baseline [66 pg/mL (37 – 93) vs 38 pg/mL (18-74), P<0.001].

Conclusions: This study is the first to report on the effect of the new drug Sacubitril/Valsartan on circulating catecholamine levels in HF patients. Our data show a significant increase in epinephrine levels during a 6 month follow up in stable HF patients.

Keywords : Sacubitril/Valsartan; angiotensin receptor neprilysin inhibitors; catecholamines; adrenergic sytem

PP18

EXPRESSION OPTIMIZATION AND PURIFICATION OF RECOMBINANT HUMAN TRUNCATED CYCLIN A AND CYCLIN D IN ESCHERICHIA COLI FOR CHARACTERIZATION WITH PUTATIVE INHIBITORS

V. Nikolopoulos, A. Grigoroudis, M. Rovoli, K. Katsoulis, G. Kontopidis

Laboratory of Biochemistry, Department of Veterinary Medicine, University of Thessaly, Karditsa, Greece

Introduction: Targeting cyclins enables us to interfere with cell cycle in order to inhibit the cancerous process, thus they have been widely held as anti-cancer targets. Seeking high levels of yield and purity, over-expression of the recombinant proteins often fail to properly fold, resulting in formation of insoluble aggregates (inclusion bodies - IB). This work attempts the over-expression of recombinant truncated forms of human Cyclin A (His-tagged CCNA2) and Cyclin D (GST-tagged CCND1) for crystallization and ligand characterization purposes.
Materials and Methods: CCNA2 and CCND1 fused to the appropriate bacterial vectors, in E. coli, as one of the most widely used expression hosts. Homogenization and sonication used to obtain the requested proteins. It is also known that co-expression with chaperone proteins facilitates their folding process, while increasing solubility in a bacterial over-expression system. Also used a number of buffer formulation for refolding purposes.
Results: BL21 (DE3) expression host is preferred for both recombinant proteins. Homogenization increases the levels of regained protein from IB. Following denaturation of IB, Urea buffer is suggested for refolding. CCNA2 and CCND1 refolding was more efficient with GSH/GSSG rather than DTT, while stability of cyclins was achieved with elevated concentrations of MgCl2. In case of CCND1 co-expression with chaperone plasmid pTf16 increases substantially soluble protein.
Conclusions: High levels of yield and purity of recombinant proteins is crucial for crystallization and ligand characterization purposes with existing synthesized peptides, designed with REPLACE (REplacement with Partial Ligand Alternatives through Computational Enrichment). This structure-activity co-relation with non-fluorescent peptides as cyclin groove putative inhibitors (CGI) where tested.

PP19

FREQUENCY DISTRIBUTION ANALYSIS OF THE rs1695 AND rs1138272 GSTP1 GENE POLYMORPHISMS IN A SOUTHEASTERN EUROPEAN POPULATION SAMPLE AND COMPARISON WITH OTHER POPULATION FREQUENCY DISTRIBUTIONS

E. Alexiou, M. S. Katsarou, R. Latsi, M. Papasavva, M. Lagiou, N. Drakoulis

Research Group of Clinical Pharmacology and Pharmacogenomics, Faculty of Pharmacy, School of Health, National and Kapodistrian University of Athens, Athens, Greece

Objective: Glutathione (GSH) is a thiol tripeptide that can be involved in the redox mechanism of cells as a reducing agent. Glutathione S-transferase P1 (GSTP1), is a member of the GSTs superfamily (which exhibit transferase properties for GSH) that protect the body from carcinogenic or genotoxic compounds. *GSTP1*polymorphisms may contribute in the development of several diseases, including cancer. Two SNPs (rs1695 and rs1138272) lead to amino acid substitutions (Ile105Val and Ala114Val) that affect the enzyme's activity by altering its ability to respond to reactive oxygen and/or nitrogen species' (ROS/RNS) activity, the causalfactor of many diseases. The frequency of GSTP1 rs1695 and rs1138272 SNPs in a Southeastern European Caucasian (SEC) population sample was studied and the results were compared with other populations (data obtained from ensembl.com).

Materials and Methods: DNA from 943 healthy, non-related SECs volunteers was collected using epithelial cells from buccal swab sampling. Genotyping was performed by real-time LightCycler 480 PCR-platform (Roche) using appropriate LightSnip Assays (TIBMOLBIOL).

Results: The frequency of the wildtype A allele of rs1695, was 72.9% (1375) and that of the G allele was 27.1% (511). Out of the 943 SECs, 54.0% (509) were homozygous for the wildtype genotype (A:A), 38.0% (357) were heterozygous (A:G) and 8.0% (77) were homozygous for the G allele (G:G). Additionally, G allele appeared 1.3 times more in Europeans than in SECs (OR=1.3314, p=0.0007). Regarding rs1138272, 88.8% (837) volunteers were homozygous for the wildtype genotype (C:C), 10.7% (101) were heterozygous (C:T) and only 0.5% (5) were homozygous for the T allele (T:T). The frequency of the wildtype C allele was 94.1% (1775) and that of the T allele was only 5.9% (111). No statistically significant difference in frequency distribution of this polymorphism was observed between SECs and Europeans. Both polymorphisms were in Hardy-Weinberg equilibrium (x^2=1.64 for rs1695 and x^2=1.04 for rs1138272).

Conclusion: As a phase II drug metabolizing enzyme, GSTP1 serves as a catalytic agent for GSH's conjugation to a variety of electrophilic substrates, an inactivating agent of a variety of antineoplastic and other drugs and an activator of antineoplastic prodrugs. Thus, *GSTP1* polymorphisms may be further investigated as pharmacotherapy biomarkers of various diseases.

PP20

FREQUENCY DISTRIBUTION OF THE ADRENERGIC RECEPTORS POLYMORPHISMS IN A SOUTH EASTERN EUROPEAN CAUCASIAN POPULATION AND THEIR CORRELATION WITH OBESITY

G. Vlachos, A. Mouchtaris-Michailidis, M. Papasavva, A. Adrianopoulou, K. Karathanosopoulou, M. S. Katsarou, M. Lagiou, N. Drakoulis

Research Group of Clinical Pharmacology and Pharmacogenomics, Faculty of Pharmacy, School of Health Science, National and Kapodistrian University of Athens, Athens, Greece

Catecholamines play a major role in the regulation of body fat. They promote lipolysis and thermogenesis through activation of the adrenergic receptors. Obesity is a multifactorial disease and the mechanisms surrounding it are not completely understood. It would be safe to assume that desensitization of the adrenergic receptors to endogenous stimuli would result in reduced fat mobilization. In the present study, we focused on polymorphismsfound in the *ADRB1* gene (rs1801252, rs1801253), the *ADRB2* gene (rs1042713, rs1042714) and the *ADRB3* gene (rs4994). These genes encode the β1, β2 and β3 adrenergic receptors respectively.

A sample of 332 volunteers who presented normal, as well as elevated BMI values, was recruited. Following informed consent, volunteer's buccal swab samples were anonymized and DNA was isolated. Genotyping was performed by melting curve analysis real-time PCR.

The results showed a statistically significant correlation of *ADRB1's* rs1801252 and rs1801253 polymorphisms with body weight gain in the groups composed of normal BMI and BMI>25 individuals. Furthermore, the appearance of rs1042713 and rs1042714 of *ADRB2* appears to statistically significant affect BMI among individuals with increased BMI (Table).

Genetic background appears to play an important role in the manifestation of obesity, so genotyping should contribute significantly to the prevention of both obesity and adverse effects on the patient's health and quality of life. Beta adrenergic receptors may play a role in BMI increasing. Further studies should be conducted to determine their mechanism of action in the development of this disease.

BMI TYPE	GENOTYPE		ODDS RATIO	95% CI	P-VALUE
	A>A (wt)	G>G & G>A			
NORMAL	35	14	3.3315	1.105-4.065	0.001
OVERWEIGHT	75	25			
NORMAL	95	14	3.069	1.064-4.000	0.05
OVERWEIGHT & OBESE I	132	41			
ADRB2 GENE (rs1801253)					
	G	C (wt)			
OBESE I	88	104	2.18	1.227-3.731	0.004
OBESE II & III	48	16			
ADRB2 GENE (rs1042714)					
	G (wt)	A			
OBESE I	101	43	1.858	1.004-2.930	0.02
OBESE II & III	55	48			
ADRB2 GENE (rs1042714)					
	CC (wt)	G & & C			
OVERWEIGHT	117	59	1.770	1.133-2.768	0.041
OBESE I	95	65			
OVERWEIGHT	88	59	1.63	0.983-2.691	0.05
OBESE II & III	46	83			

Table. Allele and genotype frequency distribution in an obese and non obese population

PP21

HISTONE DEMETHYLASE LSD1/KDM1A IS A THERAPEUTIC TARGET IN BREAST CANCER STEM CELLS

J. Verigos, D. Kordias, A. Magklara

Laboratory of Clinical Chemistry, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece & Department of Biomedical Research, Institute of Molecular Biology & Biotechnology, Foundation for Research & Technology-Hellas, Ioannina, Greece

Cancer stem cells (CSCs) or tumor initiating cells constitute an aggressive tumor subpopulation with self-renewal and differentiation properties. Resistance to conventional forms of anti-cancer treatment, disease relapse and tumor metastasis are attributed to the CSC-subpopulation making it a potential therapeutic target. To develop specific therapeutic schemes against these cells, it is important to understand the mechanisms that govern their generation and maintenance. Recent studies indicate that the unique characteristics of CSCs are under epigenetic regulation. LSD1/KDM1A (Lysine-specific histone demethylase 1) is a histone demethylase that plays an important role in oncogenesis, as it is overexpressed in many types of cancer. Recent data, also, implicate this enzyme in the regulation of breast CSCs. The aim of this study is to demonstrate that LSD1 could be a potential pharmacological target for the elimination of breast cancer stem cells.

We established and characterized an *in vitro* system of mammospheres, spheroid structures enriched in CSCs, derived from several human breast cancer cell lines. The mammosphere forming assay was used to examine the effects of LSD1 pharmacological inhibition and siRNA knock-down on the stemness properties of CSCs. The annexin V assay was used to monitor apoptotic cells. Several anti-tumor drugs were used to examine CSCs resistance to standard chemotherapy. Quantification of the CSC-subpopulation was done by FACS analysis using the $CD44^{+}/CD24^{-/low}$ phenotype.

Inhibition of LSD1 leads to a decreased ability of cells to form mammospheres, as well, as to a reduction of the $CD44^{+}/CD24^{-}$ subpopulation. Preliminary data indicate that this is not due to increased apoptosis, but rather due to increased differentiation. Treatment with anti-cancer drugs leads to enrichment of the surviving population in CSCs, while LSD1-overexpressing cells appear to have increased viability after drug administration. These data confirm that CSCs are resistant to conventional chemotherapeutic agents. Combinatory treatment with LSD1 inhibitors and anti-cancer drugs results in reduction of both non-CSCs and CSCs.

The above data support the notion that LSD1 plays an important role in the stemness properties of CSCs. Combination therapeutic schemes that also include an LSD1 inhibitor could lead to complete breast tumor elimination.

PP22

INTERLEUKIN RECEPTOR PROFILING AND TH-RELATED CYTOKINE EFFECTS IN HUMAN COLONIC SUBEPITHELIAL MYOFIBROBLASTS; POSSIBLE TARGETS FOR THERAPEUTIC STRATEGIES IN INFLAMMATORY BOWEL DISEASE

E. Filidou[1], V.Valatas[2], I.Drygiannakis[2], K.Arvanitidis[3], S. Vradelis[4], G. Kouklakis[4], G. Kolios[3]

[1] Medical School, Democritus University Of Thrace, Alexandroupolis, Greece
[2] Medical School , University Of Crete, Crete, Greece
[3] Medical School, Democritus University Of Thrace, Alexandroupolis, Greece
[4] Medical School, Democritus University Of Thrace, University Hospital Of Alexandroupolis, Alexandroupolis, Greece

Aim: Colonic subepithelial myofibroblasts (cSEMFs) have a pivotal role in the pathophysiology of fibrosis in Inflammatory Bowel Diseases (IBDs). The study's aim was to examine the expression of interleukin receptors, known to be implicated in IBD, in cSEMFs of healthy individuals (HI) and IBD patients, and how pro-inflammatory cytokines regulate their expression in HI. Furthermore, we aimed to investigate the effect of all Th-associated interleukin combinations in cSEMFs, by measuring pro-fibrotic mediators.
Methods: cSEMFs were isolated from colonic biopsies from HI and IBD patients and were screened for interleukin receptor expression using reverse transcription quantitative (RT-q) PCR. HI cSEMFs were cultured under IL-1α and/or TNF-α and interleukin receptor mRNA and protein expression was assessed at 6h and 24h using RT-q PCR and immunofluorescence, respectively. Next, HI cSEMFs were stimulated for 6h and 48h with TNF-α/IFN-γ (Th1), IL-4/IL-13 (Th2), IL-17/IL-22/IL-23 (Th17) and IL-10/TGF-β1 (Treg). Their effect on collagen, fibronectin, metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) expression was tested at 6h by RT-qPCR and at 48h by protein assays, respectively.
Results: cSEMFs exhibited basal expression levels for most interleukin receptors. IBD cSEMFs had reduced expression levels of all studied interleukin receptors compared to HI, with the exception of IL12RB2 in Ulcerative Colitis (UC) cSEMFs, which was increased. In HI cSEMFs, the expression of interleukin receptors was altered by IL1-α and TNF-α. Th1-related cytokines upregulated collagen, fibronectin and MMP-1 expression and downregulated MMP-9. Th2-related cytokines upregulated collagen and MMP-1 expression and downregulated fibronectin and MMP-9 expression. Th17-related cytokines had a mixed effect in cSEMFs; IL-17 and IL-23 upregulated fibronectin, while IL-22 suppressed its expression. IL-23 upregulated both MMP-1 and TIMP-1 expression. TGF-β was the most potent pro-fibrotic agent, as it upregulated all studied fibrotic factors.
Conclusions: Our results suggest that cSEMFs are directly implicated inflammation and fibrosis, as they exhibit a rich expression panel of Th-related interleukin receptors, making them responsive to cytokines, abundant in the inflamed mucosa of IBD patients. Similar to TGF-β, IL-23 exhibited the most pro-fibrotic effects on cSEMFs, highlighting it as a possible target for therapeutic strategies in the treatment of fibrosis.

PP23

ISOLATION AND CHARACTERIZATION OF BACTERIOPHAGES AGAINST BACTERIAL PATHOGENS

P. Bozidis, A. Vasiliadis, H. Sakkas, C. Papadopoulou

Department of Microbiology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Background: Lytic bacteriophages are viruses that can infect and eliminate bacteria. The application of phages to selectively reduce or destroy susceptible pathogens from specific environments is called phage therapy. Phage therapy may be a suitable alternative to antibiotic treatment due to the high specificity and effectiveness against multi drug resistant bacteria.

Objectives: The aim of this study was the isolation and characterization of lytic bacteriophages against reference strains and clinical isolates of *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* from raw sewage of a tertiary hospital.

Material and Methods: Six samples of the hospital waste water treatment plant input were collected during three months period (January – March 2018). Sewage was centrifuged for the separation of soluble and insoluble fractions. Both fractions were processed accordingly. Each fraction was mixed with equal volume of an overnight culture of the corresponding bacterial strain in Mueller-Hinton Broth (MHB) and was left for 4h at 37^{0}C for phage enrichment. Phage activity was detected by spot assay and plaque assay using the double-layer agar overlay technique. Single plaques were picked with sterile glass Pasteur pipettes and were inoculated into log phase cultures of the same bacterial strain in order to purify the bacteriophages. DNA was extracted from purified bacteriophages and examined by restriction enzyme digestion and gel electrophoresis. The protein composition of bacteriophages was examined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) followed by Coomassie blue staining.

Results: Four lytic bacteriophages against *Escherichia coli* reference and clinical strains were isolated; however, no bacteriophages against other tested bacterial strains were identified Further tests for characterization of the four isolated coliphages in terms of host range, thermal and pH sensitivity, morphology, genome and protein composition are in process.

PP24

NUTRIRIONAL DISORDERS IMPAIR THE ONE-CARBON CYCLE AND INFLUENCE THE DIABETIC CARDIOMYOPATHY REMODELING

A. Al Humadi[1], A. Strilakou[1], I. Mourouzis[1], E. Agapitos[2], P. Karkakousos[3], C. Liapi[1]

[1] Department of Pharmacology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[2] 1st Department of Pathology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[3] Department of Medical Laboratories, Technological Institute of Athens, Athens, Greece

Background: Choline is recognized as an essential nutrient for public health with crucial role in the pathway of one-carbon metabolism. Its deficiency setting is an established experimental model of non-alcoholic steatohepatitis resembling the human non-alcoholic fatty liver disease (NAFLD), which is associated with increased morbidity and mortality due to cardiovascular disease (CVD). NAFLD is also predisposed by diabetes and vice versa, while diabetic cardiomyopathy manifestations include left ventricular hypertrophy and diastolic dysfunction.

The aim of this study was to evaluate cardiac remodeling process in the case of concomitant conditions of choline deficiency and diabetes.

Material and methods: 24 Wistar Albino rats (about 3 months old) were divided randomly into rats fed with standard (C) or choline deficient diet (CDD) and diabetic rats fed with standard (DM) or choline deficient diet (CDD+DM). Diabetes was experimentally induced by intraperitoneal injection of streptozotocin at a dose of 50 mg/kg body weight. After one month of dietary intervention cardiac function was evaluated by echocardiography study, which was followed by a histopathology evaluation in order to investigate the structural tissue abnormalities of the myocardium.

Results: Echocardiography evaluation revealed dilation of the left atrium in the CDD+DM group accompanied by a decrease of the left ventricular wall thickness ($p=0.041$ vs DM, $p=0.009$ vs CDD and $p=0.015$ vs C) with preserved ejection fraction. Histological examination showed inflammatory and fibrotic lesions in the choline-deprived diabetic rats that were more extended in comparison to diabetic only ($p<0.001$).

Conclusions: Cardiomyopathy induced by both choline deficiency and diabetes conditions follows an intriguing pattern with restrictive and dilated features at the same time suggesting that this setting promotes cardiac reserve depletion triggering earlier the exacerbation of cardiac performance in both the systole and diastole. Further studies are necessary to shed light to the implicated pathophysiological mechanisms.

PP25

PANCREATIC-SPECIFIC GENE METHYLATION DETECTED IN LIQUID BIOPSIES AS A MONITORING BIOMARKER OF B-CELL DEATH IN TYPE II DIABETES

M. Karaglani[1], M. Panagopoulou[1], M. Markaki[2], I. Balgkouranidou[1], E. Nena[3], G. Kolios[1], E. G. Manolopoulos[1], I. Tsamardinos[2,4], E. Maltezos[5], N. Papanas[5], G. Mastorakos[6], E. Chatzaki[1]

[1] Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Democritus University of Thrace, Alexandroupolis, Greece

[2] Department of Computer Science, University of Crete, Heraklion, Crete, Greece

[3] Laboratory of Hygiene and Environmental Protection, Faculty of Medicine, School of Health Sciences, Democritus University of Thrace, Alexandroupolis, Greece

[4] Gnosis Data Analysis PC, Heraklion, Crete, Greece

[5] Diabetes Center, 2nd Department of Internal Medicine, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis, Greece

[6] Endocrine Unit, 2nd Department of Obstetrics and Gynecology, National & Kapodistrian University of Athens, "Aretaieion" University Hospital of Athens, Athens, Greece

Aim: DNA Methylation is an epigenetic event that regulates tissue-specific gene expression. Typical examples are insulin, amylin and glucokinase genes that are exclusively unmethylated (transcriptionally active) in pancreatic β-cells and methylated (transcriptionally inactive) in the rest of the body's cells. Such tissue-specific methylation motifs make it possible to use differentially methylated DNA as a diagnostic tool. The cell-free circulating DNA (ccfDNA) of serum is a minimally invasive "wet biopsy" that appears to reliably reflect the tissue-specific epigenetic modifications of the tissue from which it originates. Our goal in the present study is to describe β-cell specific methylation patterns of ccfDNA in sera of type 2 diabetes mellitus (TDM2) patients in order to demonstrate its β-pancreatic origin and to evaluate its ability to quantitatively reflect the progression of pancreatic lesion, an important and clinically useful parameter in the management of the disease.

Methods: Total serum ccfDNA was quantified in 96 TDM2 patients and 71 age-matched healthy volunteers. This was followed by isolation and characterization by capillary electrophoresis, treatment with sodium bisulfite and quantitation of methylation of pancreatic β-cell genes insulin (INS), amylin (IAPP) and glucokinase (GCK) with quantitative Methylation Specific PCR (qMSP).

Results: Total ccfDNA levels did not differ between TDM2 patients and healthy volunteers. Capillary electrophoresis revealed DNA fragment size of 180 bases and multiples mostly in the patients' group, indicating release during of β-pancreatic cellular apoptosis. The qMSP methods were evaluated for their sensitivity and specificity. Elevated levels of unmethylated alleles of the insulin and amylin gene were observed in the serum of patients compared to healthy volunteers, indicating loss of β-pancreatic cells, and were higher in patients presenting T2D complications. Insulin-treated patients had lower levels of β-pancreatic ccfDNA, possibly due to already extensive tissue damage.

Conclusions: Tissue-specific methylation of β-pancreatic genes is detected in patient serum ccfDNA. It can thus provide a quantitative minimally invasive approach for the dynamic monitoring of β-pancreatic cell loss and progression of the disease in order to guide treatment options.

PP26

PERSONALIZED THERAPY OF FOCAL IMPAIRED AWARENESS SEIZURES BASED ON GENOTYPING OF GENE SCN1A- PRELIMINARY RESULTS

E. Kokkiou[1], M. Katsarou[1], A. Siatouni[2], S. Gatzonis[2], M. Koutsilieris[3], I. Sakkas[3], A. Alexoudi[2], A. Verentzioti[2], P. Patrikelis[2], N. Drakoulis[1]

[1] Research Group of Clinical Pharmacology and Pharmacogenomics, Faculty of Pharmacy, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[2] A' Department of Neurosurgery, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

[3] Department of Experimental Physiology, Faculty of Medicine, School of Health Sciences, National & Kapodistrian University of Athens, Athens, Greece

Purpose: Clinically, SCN1A gene is the most important epilepsy related gene. SCN1A gene encodes the alpha subunit of the neuronal voltage-gated sodium channels in the brain, known as Nav1.1. Genetic polymorphisms in this gene have been involved in epileptogenesis and different epilepsy phenotypes. SCN1A protein, also plays a major role as antiepileptic drug target. The aim of this study is to investigate 3 common polymorphisms of SCN1A gene and their role both in drug responsiveness in antiepileptic therapy and susceptibility in Focal impaired awareness seizures (FIAS).

Methods: DNA samples from southeastern European Caucasians drug-responsive and drug-resistant epileptic patients with FIAS analyzed with real-time PCR for polymorphisms rs2298771, rs3812718 and rs10188577. Additionally, from Ensemble database, data from 503 individuals used as controls. Chi-square test used to evaluate the correlation of these polymorphisms with FIAS susceptibility and drug responsiveness. All samples were anonymized, randomized and de-identificated after an inform consent was signed by each patient.

Results: AA & GG genotypes of rs2298771 appear 2 times more often in epileptic patients with FIAS than in General population (p=0.003). Furthermore, individuals with a specific combination of polymorphisms of SCN1A gene seem to have different response to therapeutic anti-epileptic agents. In this study, 60% of patients with genotypic combination of AA/TC/TT of rs2298771/rs3812718/rs10188577, respectively responded well to therapy. In contrast, 80% of patients with genotypic combination AG/CC/TT of rs2298771/rs3812718/rs10188577, respectively were poor responders to therapy.

Conclusions: There is a correlation between rs2298771 G allele and susceptibility in FIAS. Genotyping of SCN1A gene before initiating any anti-epileptic medication may contribute to personalization epileptic therapy of FIAS. Further investigation in larger groups of patients will validate these results.

PP27

PHARMACOLOGICAL ASSESSMENT OF SMALL-MOLECULE PROTEIN METHYLTRANSFERASE INHIBITORS ON ERYTHROID MATURATION IN VITRO

N. Theodoroula, M. Akrivou, I. Vizirianakis

"Aristotle" University of Thessaloniki, Thessaloniki, Greece

Epigenetic mechanisms play a crucial role in the regulation of gene expression in a way that their deregulation contributes to disease pathogenesis and progression. Several drugs have entered the market that target epigenetic enzymes, whereas more chemical entities are under development and clinical trials. Recent research efforts in cancer therapy focus on developing new innovative small-molecule inhibitors targeting protein methyltransferases (PMTs). In the present work, the main aim was to assess the effect of twelve selective inhibitors targeting various PMTs onerythroidmaturationcell model systems.Murine erythroleukemia(MEL) cells were treated separately with each one of the twelve PMTs inhibitors to estimate: a) the dose-dependent cytotoxicity profileof the compounds and their IC50 values; b) the potential to induce differentiation of MEL cells to erythroid maturation; c) the ability to work synergistically with the known chemical inducer HMBA to induce commitment of cells to erythroid maturation; d) the ability of cells to enter the various phases of cell cycle upon differentiation.Based on the data obtained, three of PMTs inhibitors targeting G9a were selected for further investigation in the K-562 cell model system. In this regard, the treated K-562 were then assessed to estimate: a) their cellular growth capacity;b) cell cycle phase distribution; and d) gene expression profiles in a panel of molecules involved in crucial cell decisions for proliferation, differentiation and/or apoptosis. The data obtained thus far indicate thatthe twelve PMTs inhibitors under investigation: a) present heterogeneity in their MEL cell cytotoxicity profile; b) cause cellular phenotype alterations coinciding with their cytotoxicity behavior; c) alter the cell cycle phase distribution profile; d) show variability in their synergistic capacity to modulate HMBA-induced MEL erythroid maturation; e) the three G9a inhibitors exhibit different cytotoxicity effects and morphological changes in K-562 cells with an interesting potential to affect cell cycle phase distribution and modulate gene expression profiling in culture.Overall, the results obtained give new insights on how small-molecule specific inhibitors targeting various PMTs can affect cellular decisions in erythroleukemia cells, a fact of crucial importance upon the pharmacological development of new innovative anticancer therapeutics.

PP28

EFFECTS OF SIDERITIS SCARDICA (MOUNTAIN TEA) CONSUMPTION ON THE ACTIVITIES OF CYP1A2, CYP2A6, XANTHINE OXIDASE (XO), N-ACETYLTRANSFERASE-2 (NAT2) AND UDP-GLUCURONOSYLTRANSFERASES-1A1/1A6 (UGT1A1/1A6) IN HEALTHY VOLUNTEERS

E. Begas[1], A. Tsioutsioumi[1], I. Charitou[2], E. Asprodini[1]

[1]Laboratory of Pharmacology, Department of Medicine, University of Thessaly, Larissa, Greece
[2] Oncology Clinic, University Hospital, Larissa, Greece

Aims: Sideritis Scardica (mountain tea, SS) is an endemic plant of the rocky areas and alpine regions of the Balkan peninsula traditionally used as herbal tea for inflammation, coughing and gastric disorders. Previous in vitro and in vivo studies have shown that aqueous extracts of various herbs affect the activity of Phase I and Phase II enzymes in xenobiotics metabolism. However, there is no in vivo study addressing the effects of the SS decoction on the activity of these enzymes in humans. The purpose of the present study was to investigate the effects of SS decoction on the functionality of CYP1A2, CYP2A6, XO, NAT2 and UGT1A1/1A6 enzymes in healthy volunteers.

Materials-Methods: Fifteen healthy volunteers consumed SS collected from Olympus mountain (4g of dry product/200mL of water, twice daily) for six days. The volunteers were administered caffeine as probe-drug for CYP1A2, CYP2A6, XO and NAT2 and paracetamol for UGT1A1/1A6 functionality. Enzyme activities were determined before and at the end of the study period using the following caffeine and paracetamol metabolites concentration ratios measured by HPLC: CYP1A2: 1,7-dimethylxanthine/caffeine (saliva) and (5-acetylamino-6-formylamino-3-methyluracil+1-methyluric acid+1-methylxanthine)/1,7-dimethyluric acid (urine); CYP2A6: 1,7-dimethyluric acid /(1,7-dimethyluric acid+1,7-dimethylxanthine), XO: 1-methyluric acid/(1-methyluric acid+1-methylxanthine), NAT2: (5-acetylamino-6-formylamino-3-methyluracil)/(5-acetylamino-6-formylamino-3-methyluracil+1-methyluric acid+1-methylxanthine) and UGT1A1/1A6: glucuronidated/total paracetamol, all determined in urine.

Results: CYP1A2 urine and saliva indices decreased after the consumption of SS yet the difference was significant only in saliva metabolite ratios (3.87±0.65 vs 3.63±0.70, $p>0.05$; 0.56±0.20 versus 0.44±0.10, $p=0.044$). CYP2A6 urine metabolite ratio exhibited a marginal decrease after the consumption of SS (0.77±0.08 versus 0.73±0.09; $p=0.057$). XO urine metabolite ratio remained unaltered after the consumption of SS (0.67±0.05 versus 0.66±0.06; $p>0.05$). NAT2 index in urine remained unchanged after the consumption of SS (0.27±0.18 versus 0.26±0.18; $p>0.05$). UGT1A1/1A6 index in urine exhibited a non significant increase after the consumption of SS (0.75±0.14 versus 0.81±0.12, $p>0.05$).

Conclusion: Regular consumption of SS decoction appears to significantly inhibit CYP1A2, mainly, and CYP2A6, secondarily, in vivo activities. No significant effects on XO, NAT2 or UGT1A1/1A6 activities were observed. This effect may alter the pharmacokinetics of clinically administered drugs and promote cancer chemoprevention through CYP1A2 and CYP2A6 inhibition.

POSTERS SESSION B'

PP29

PLACEBO EFFECT IN PAIN RELIEF AND CLASSICAL CONDITION

D. Skavatsos, S. Kokkinos, C. Triantis

Pharmacy Department, Frederick University, Nicosia, Cyprus

Aim: The aim of this work is to examine the role of the placebo effect in pain relief, immune and hormonal responses.

Methods: A bibliographic research took place, using the terms "placebo, placebo effect, analgesia and classical condition" as keywords through PubMed and Scopus.

Results: A common practice in clinical trials is the use of use placebo in order to investigate the effect of new compounds. A cohort of patients receiving a new drug, whereas the remaining patients the placebo (double-blind study). Comparing both the drug and placebo, the efficacy and safety of the new compound are determined. Placebo's mechanism of action focuses on patient's expectations and beliefs about the disease. In particular, when a patient expects that the treatment will have a positive effect, the body's chemistry produces therapeutic signals similar to these caused by the respective drugs. The first element studied in detail is the placebo analgesia. Administration of placebo causes an increased release of endorphins in the brain, which are natural body's painkillers that activate endogenous receptors to relieve a painful stimulus. Beyond neurobiological mechanisms, the effect of placebo analgesia could also be explained by the subjective perception of pain. In addition, placebo effect can be useful in cardiologic or cancer patients, to make them feel better and reduce the side effects from the NSAIDs or opiates, but not to solve their problems. Classical condition plays a major role in the placebo effect. This condition contributes to unconscious psychological functions like immune and hormonal system. In classical conditioning, after repeated administrations of a conditioned stimulus (CS) (e.g. inactive agent) and unconditioned stimulus (US) (e.g. active agent), the CS can induce a conditional response that it is similar to that induced by the active drug.

Conclusion: The role of the placebo plays a major role in clinical trials for the evaluation of new drugs as well as in therapeutics. It constitutes an indication that organism contributes to the disease's treatment through the appropriate suggestions.

PP30

POLYPHARMACY AND EXTENDED POLYPHARMACY AMONG OLDER PEOPLE IN THESSALONIKI, GREECE

M. Michailidou[1,2], P. Papaioannidou[1]

[1] 1st Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] Clinical Pharmacology and Therapeutics, Faculty of Medicine, School of Health Sciences, Democritus University of Thrace, Alexandroupolis, Greece

Aim: The aim of this study was to explore polypharmacy and extended polypharmacy among older people in the community of Thessaloniki, Greece.

Methods: The sample was collected using the new Electronic Health Records that have been applied in the last years in Greece. All prescriptions concerning patients older than 65 years and dispensed during April 2017 in a pharmacy store of western Thessaloniki were used. In order to include non prescribed medications, we kept a record of medications bought by the patients without prescription, and we also asked them directly about the use of other medications.

Results: Out of 800 prescriptions we collected 440 prescriptions concerning 210 patients older than 65 years (mean age 77 years, range 65-99). 44% of them were male and 56% of them were female. Polypharmacy ($\geqslant$ 5 medications) was observed in 55% of patients (of whom 42% were male and 58% female). Extended polypharmacy ($\geqslant$ 10 medications) was observed in 14% of patients (of whom 48% were male and 52% female). The most commonly used medication groups were cardiovascular, analgesic, hypolipidemic, antiulcer, anticoagulant / antiplatelet, and antidiabetic medications. Although analgesics were second in the frequency of usage, some of them were not included in prescriptions, as they are not reimbursed by the National Health System (NHS). Even medicines reimbursed by the NHS (like thyroid hormones) were not included in prescriptions, either because they are cheap and can be bought without prescription or because patients can't afford going to doctor, due to the financial crisis.

Conclusions: Polypharmacy is common among older people in Greece, with 55% of them using 5 or more medications. Extended polypharmacy, with use of 10 or more medications is not so common, reaching a percentage of 14%. In order to record actual polypharmacy, apart from the Electronic Health Records, it is necessary to collect data directly from the patients. Polypharmacy and extended polypharmacy may increase drug interactions and pharmaceutical adverse reactions, and may augment the risk of unplanned hospital admissions and the burden of medicinal cost.

PP31

POPULATION-BASED ANALYSIS OF THE FREQUENCY OF CYP2C9 (RS1799853, RS1057910), CYP2C19 (RS4244285), CYP1A2 (RS762551), CYP11B2 (RS1799998), CYP17 (RS619824) GENE POLYMORPHISMS IN A SOUTHEASTERN EUROPEAN CAUCASIAN POPULATION

G. Diles, D. Theodoridou, M. Papasavva, M. S. Katsarou, M. Lagiou, T. Kalogridis, N. Drakoulis

Research Group of Clinical Pharmacology and Pharmacogenomics, Faculty of Pharmacy, School of Health Science, National and Kapodistrian University of Athens, Athens, Greece

Important phase I drug metabolizing Cytochrome P-450 enzymes (CYPs) are involved in the metabolism of xenobiotics as well as endogenous substrates including cholesterol, steroids and other lipids. Genetic polymorphisms within CYPs affect drug metabolism, leading to differences in drug response. A frequency distribution analysis of the polymorphisms *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910), *CYP2C19*2*(rs4244285), *CYP1A2*1F* (rs762551), *CYP11B2* (rs1799998) and *CYP17A1* (rs619824) in a Southeastern European Caucasian population was performed. *CYP2C9*2*, *CYP2C9*3* and *CYP2C19**2 are related with reduced enzyme activity, thus *CYP1A2*1F* is related with high enzyme activity. *CYP11B2* polymorphism leads to increased aldosterone to rennin ratio.

DNA was extracted by buccal swabs of 534 non related SEC's and genotyping was performed by real time PCR (Light Cycler 480, Roche) using appropriate LightSnip Assays (TIBMOLBIOL).

The allele and genotype frequency distribution in our SEC population is cited in Table 1.

For *CYP2C9*2*, *CYP2C9*3*, *CYP2C19*2* and *CYP1A2*1F*, statistically significant differences between Southeastern European Caucasian and African, American, East Asian and South Asian populations were observed, whereas, for *CYP11B2* statistically significant differences between Southeastern European Caucasian and African, other European and East Asian populations were observed. For *CYP17A1* statistically significant differences between Southeastern European Caucasians and African and East Asian populations were observed.

Adjustment of the drug dosage should be taken into consideration because of the differences between populations. The genotyping analysis of these polymorphisms plays a significant role in the overall treatment of patients and contributes to personalised pharmacotherapy.

Gene	Single Nucleotide Polymorphism	Wild type homozygous	Heterozygous	Mutant homozygous	Wild type
CYP2C9	rs1799853	CC=74.2%	CT=23.2%	TT=2.6%	C=85.8%
CYP2C9	rs1057910	AA=83.9%	AC=15.7%	CC=0.3%	A=91.8%
CYP2C19	rs4244285	GG=71.5%	GA=27.8%	AA=0.6%	G=85.4%
CYP1A2	rs762551	CC=7.1%	CA=43.1%	AA=49.8%	C=28.7%
CYP11B2	rs1799998	TT=52.8%	TC=38.2%	CC=9.1%	T=71.9%
CYP17A1	rs619824	TT=34.4%	TG=50.6%	GG=20.6%	T=45.4%

Table 1. Allele and genotype frequency distribution in SEC population.

PP32

POPULATION-BASED ANALYSIS OF TNF-A, IL6 AND CRP GENE FREQUENCY POLYMORPHISMS IN SOUTH EASTERN EUROPEAN CAUCASIAN POPULATION SAMPLE AND CORRELATION WITH INFLAMMATION SUSCEPTIBILITY

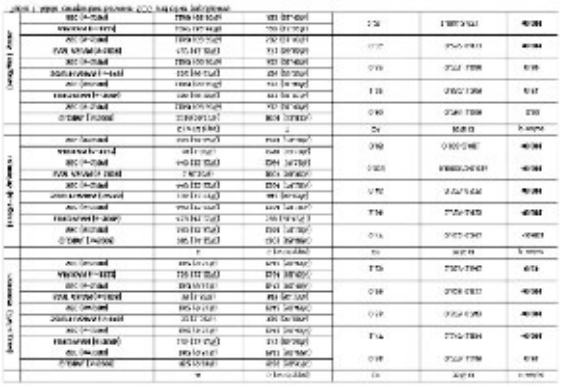
A. Petraina, E. Georgiadi, M. S. Katsarou, M. Papasavva, M. Lagiou, T. Kalogridis, N. Drakoulis

Research Group of Clinical Pharmacology and Pharmacogenomics, Faculty of Pharmacy, School of Health Science, National and Kapodistrian University of Athens, Athens, Greece

Inflammation is a complicated, well-orchestrated process by a variety of cells and chemical mediators such as TNF-a, IL-6 and CRP. The less common A allele of *TNF-a* gene polymorphism rs1800629 seems to increase TNF expression levels. The mutated C allele of *IL-6* gene polymorphism rs1800795 and T allele of *CRP* gene polymorphism rs1205 are related to lower levels of IL-6 and CRP, respectively.

A frequency distribution analysis of rs1800629, rs1800795 and rs1205 polymorphisms in a South Eastern European Caucasian (SEC) population sample was performed. DNA from buccal swabs of 852 non related SEC was collected and analysed. Gene distribution for polymorphism rs1800629 was G:G=81.8%, G:A=17.4% and A:A=0.8. The wild-type G allele frequency was 90.5%. Frequencies for rs1800795 were G:G=54.8%, G:C=38.7% and C:C=6,5%. The wild-type G allele frequency was 74.2%. The frequencies for rs1205 were C:C=47.7%, C:T=41.9% and T:T =10.4%. The wild-type C allele frequency was 68.6%. The frequency distribution of all analysed polymorphisms of the SEC population differs significantly when compared with other populations (SEC v/s Europeans, Africans, East Asians and South Asians. for rs1800629, v/s global, Europeans, Africans, East Asians and South Asians for rs1800795 and v/s Africans and East Asians for rs1205). Although not statistically significant, the investigated SEC population has great similarity to the global population regarding the allele distribution of rs1800629 and to the European and South Asian population regarding the allele distribution of rs1205.

Inflammation is affected by multiple factors; however, the genotyping analysis of polymorphisms may play a significant role in susceptibility of inflammation.



PP33

PRENATAL ETHANOL EXPOSURE ALTERS THE EXCITATORY AND INHIBITORY CONTROL OF SYNCHRONOUS EPILEPTIFORM DISCHARGES RECORDED IN JUVENILE RAT HIPPOCAMPAL SLICES

M. E. Evangelaki, I. Papasideri, F. Y. Kattan, C. Psarropoulou

Department of Biological Applications and Technology, School of Health Sciences, University of Ioannina, Ioannina, Greece

Aim: Fetal Alcohol Syndrome (FAS) is a neurotoxic syndrome resulting from exposure of a fetus to alcohol during pregnancy and is associated with several long-term neurological abnormalities, including the increased susceptibility to epileptic seizures in the offspring. The aim of this study was to investigate the effects of prenatal ethanol exposure on the control of synchronous interictal-like epileptiform discharges (IEDs) by inhibitory ($GABA_A$R-) and excitatory (NMDAR-mediated) mechanisms on hippocampal slices,

Methods: Female Sprague-Dawley rats were given a solution of 15% v/v ethanol as their only source of drinking water before, throughout gestation and up to postnatal day (PD) 15 of the offspring, that were subsequently sacrificed at PD 21-35 to prepare temporal hippocampal slices from which to record extracellularly (FAS-slices); control slices were originated from identical-age normal rat pups (N-slices). Spontaneous IEDs, induced by perfusion with Mg^{2+}-free ACSF (=NMDA-R activation) were recorded from the CA1 area.

Results: Mg^{2+}-free ACSF perfusion induced IEDs in all (151 N, 115 FAS) slices, with significantly lower frequency in FAS (0.16±0.01 Hz) compared to N (0.24 ±0.01 Hz, p=0.002). The $GABA_A$-R antagonist BMI (20μM) decreased IED frequency in 29/37 N (p<0.0001) and 28/55 FAS slices (p<0.0001) and increased it in the remaining, showing an IED frequency decrease in N (p=0.0077) and an increase (trend) in FAS slices. BMI increased IED duration in N slices (by 346±36.16, n=25, p=0.012) only. The non-NMDA-R antagonist CNQX (20μM) depressed IED frequency significantly and marginally more in N slices (p=0.04; N by 30-87%, n=6, p<0.005l; FAS by 23-42%, n=4, p=0.01). In the presence of BMI, CNQX depressed IED frequency less, and significantly so only in N slices (p=0.01). The NMDA receptor antagonist APV (50μM) depressed significantly IED frequency in N=19 and FAS=30 slices, an effect more pronounced in the latter (p=0.03). In the presence of CNQX, APV blocked all remaining activity (5N and 4FAS slices).

Discussion: Prenatal ethanol exposure leads to detectable *in vitro* changes in the control of synchronous hippocampal epileptiform discharges: Synaptic inhibition appears to be reduced, interneuron excitation (non-NMDA-Rs) appears to be increased and NMDA-Rs affect synchronization mechanisms more.

PP34

PREVALENCE OF MULTIDRUG-RESISTANT BACTERIA ISOLATED FROM WASTEWATER TREATMENT PLANTS

H. Sakkas, A. Ilia, G. Mpekoulis, P. Bozidis, C. Papadopoulou

Microbiology Department, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Objectives: Over the past years, there is a continuously recorded increase in antimicrobial resistance caused by the wide spread of antimicrobials both clinically and environmentally. Several studies have disclosed the presence of resistant microorganisms in environmental samples collected from river and surface water ecosystems, wastewaters, plants and soils. The aim of this study was to determine the occurrence of multidrug-resistant bacteria in raw sewage samples from of a tertiary hospital focusing on the ESKAPE bacteria (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species*) and the comparison of the antibiotic resistance profile of the isolated strains.

Material and Methods: Hospital raw sewage samples of 0.5 L each were collected into sterile bottles, transported to the laboratory on ice packs in portable insulated containers and processed within 24 h. Samples were concentrated using the filtration technique onto 0.45-μm pore size filter membranes. Membranes were placed onto the surface of differential selective agars (MacConkey, Chapman and Bile esculin media) and selective chromogenic agars (*S. aureus*, VRE, ESBL, KPC and*Pseudomonas* chromogenic media), and were incubated for 24-48 h at 37 °C in air. The API system was used for strain identification, and antimicrobial susceptibility testing was performed using the Kirby-Bauer diffusion method and the E-test assay according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Results: The isolated Gram positive (*Staphylococcus aureus*, *Enterococcus* spp) and Gram negative (*Escherichia coli*,*Klebsiella* spp, *Pseudomonas aeruginosa*, *Acinetobacter* spp, *Enterobacter* spp) bacteria demonstrated significant resistance to the majority of tested antibiotics.

Conclusions: Multidrug-resistant bacteria have become a major global threat causing severe healthcare-acquired infections with limited antimicrobial treatment options. Our results confirmed that there is a large and divergent gene pool encoding for multidrug-resistance within hospital environments.

PP35

PSYCHOTROPIC DRUGS EFFECT IN HUMAN LYMPHOCYTES FROM PATIENTS WITH AUTOIMMUNE DISEASES

G. Demirtzoglou[1], S. I. Chrysoglou[1], A. Theodoridou[2], A. Garyfallos [2], Z. Iakovidou Kritsi[1], A. Lambropoulos[1]

[1] Laboratory of Medical Biology and Genetics, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] 4th Department of Internal Medicine, "Hippokration" General Hospital of Thessaloniki, Thessaloniki, Greece

Objectives: The aim of the present study was to investigate how T and B lymphocytes' DNA is affected by three psychotropic drugs in healthy donors, patients with Systematic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA).

Methods: The effect of two antipsychotic drugs (haloperidol, olanzapine) and one antidepressant drug (venlafaxine) on Sister Chromatid Exchanges (SCEs), Proliferation Rate Index (PRI) and Mitotic Index (MI) was investigated. SCEs are considered as one of the most sensitive markers of genotoxicity, PRI is one of the most reliable markers of cytostatic activity, whereas MI shows precisely the ability of the cell to proliferate.

Blood given by eight healthy donors, eight patients with SLE and eight patients with RA was used for the isolation and cultivation of T and B lymphocytes for the SCE, PRI and MI assays. Three different concentrations' solutions of each drug were prepared and tested for each drug. Statistical analysis took place using SPSS 23.0. Mann-Whitney U test was used for all the indices as well as Kruskal – Wallis test for the evaluation of each concentration.

Results: Analysis of the results for haloperidol has revealed a statistically significant ($p < 0.001$) dose-dependent increase of SCEs in healthy donors, and a reduction in lowest concentration in SLE patients for both T and B lymphocytes. SCEs in RA patients did not seem to be affected in B lymphocyte assay. PRI and MI values dropped for both healthy donors and patients in the highest therapeutic concentrations. Olanzapine and venlafaxine caused a significant induction of SCEs values in SLE and RA groups in the highest concentrations but only venlafaxine caused a reduction in B lymphocytes' SCEs at lowest concentration in SLE group. Finally, olanzapine reduced SCEs values of T lymphocytes in SLE patients, but not in healthy donors and RA patients in the lowest therapeutic doses.

Conclusions: Cytogenetic differences concerning SCEs between T and B lymphocytes in SLE group need further investigation as B lymphocytes are cytogenetically more stable than T lymphocytes and these findings may indicate a different mechanism of action of the drug and a clue for the pathogenesis of SLE.

PP36

SCREENING HUMAN HAIR FOR 132 NOVEL PSYCHOACTIVE SUBSTANCES (NPS) BY TANDEM LC/MS: TRENDS AND CHALLENGES

V. Boumba[1,3], M. Di Rago[1,2], M. Peka[2], O. Drummer[1], D. Gerostamoulos[1,2]

[1] *Department of Forensic Medicine, Monash University, Australia*

[2] *Victorian Institute of Forensic Medicine, Australia*

[3] *Laboratory of Forensic Medicine & Toxicology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece*

Introduction: Novel Psychoactive Substances (NPS) are now frequently encountered in forensic toxicology investigations while their number introduced in the grey market each year is constantly increasing, challenging toxicologists to expand their analytical demands. Hair testing for drugs is well established in forensic and clinical toxicology fields, however, limited screening procedures for NPS currently exist and most of them are restricted to certain classes of NPS, contain limited numbers of NPS and require time consuming sample preparation.

Objective: The development and validation of a liquid chromatography / tandem mass spectrometry multi-analyte method to qualitatively identify (screening) NPS of different classes in hair utilizing a single extraction step.

Methods: An aliquot of washed hair was pulverized with 0.1 M hydrochloric acid (concentrated) / methanol, centrifuged, supernatants were evaporated to dryness and finally, reconstituted with methanol. LC-MS/MS system followed in MRM mode using positive electrospray ionization. Separation was performed with gradient elution and run time of 12.40 min.

Results: The limit of reporting was set at 0.1 ng/mg. Matrix effects were acceptable for most NPS, both at low and high concentration. Ion enhancement (>125 %) was observed at high concentrations for benzylpiperazine, pseudo-ephedrine, ethylone, PPP, and MDPPP. All analytes showed variation in response within 20 % of the mean. Extraction efficiencies were above 75 % for most analytes. The lowest values in extraction efficiencies were observed for cathinones and piperazines while most synthetic cannabinoids showed excellent extraction efficiencies. Hair samples from 23 coronial cases where NPS were detected in blood or where NPS abuse was suspected were tested. Many NPS were identified including acetyl fentanyl, 25C?NBOMe, MDPV, PB-22 and AB-FUBINACA, confirming hair as a useful matrix for the analysis of NPS where historical or retrospective information is sought.

Conclusion. A rapid tandem LC-MS method for the targeted screening of 132 NPS in hair was developed that covers a broad range of NPS, mainly synthetic cathinones and synthetic cannabinoids, but also amphetamine type designer drugs, piperazines and other hallucinogenic compounds. The method can be used in routine medico-legal toxicology investigations and it provides the potential to include screening for more NPS in future applications.

Keywords (3) Novel psychoactive substances (NPS); hair; LC-MS/MS

PP37

THE ROLE OF RPTPB/Z IN THE CARDIAC FUNCTION IN VIVO

D. Bousis[1], P. Castana[1], A. Varela[2], C. H. Davos[2], G. Tsigkas[3], P. A. Davlouros[3], E. Papadimitriou[1]

[1] *Laboratory of Molecular Pharmacology, Faculty of Pharmacy, School of Health Sciences, University of Patras, Patras, Greece*

[2] *Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, Athens, Greece*

[3] *Department of Cardiology, Patras University Hospital, Patras, Greece*

Aim: RPTPβ/ζ is a transmembrane tyrosine phosphatase receptor that is involved in the development of the central nervous system and is also extensively investigated as a regulator in the development and growth of malignant tumors, as well as angiogenesis. Heart failure is a severe clinical condition with high morbidity and mortality rate, which affects a constantly increasing number of patients worldwide. Pathologically, there is evidence of an attenuated angiogenesis in the failing myocardium which night be a potential target for future therapeutic interventions for heart failure. This study aims to investigate the impact of RPTPβ/ζ in the cardiac function *in vivo* and investigate a potential link with angiogenesis through molecular pathways.

Materials and methods: Genetically modified mice not expressing RPTPβ/ζ ($Ptprz^{-/-}$) were used and compared with the corresponding wild-type mice ($Ptprz^{+/+}$). Paraffin-embedded cardiac tissue sections of mice were stained with *Wheat germ agglutinin* and *Griffonia Simplicifolia* lectins to study cardiomyocyte volume and number of vessels respectively. The images acquired from confocal microscope were analyzed with the Image J software. Echocardiography study of the left ventricle (LV) was performed in six $Ptprz^{+/+}$ and six $Ptprz^{-/-}$ mice (VEVO2100, Visual Sonics). M-mode measurements of LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD) and the percentage of LV Fractional Shortening (FS%) = [(EDD-ESD)/EDD] x 100 were calculated. Western blot analysis for extracellular matrix and signalling molecules linked to regulation of angiogenesis was also performed.

Results: $Ptprz^{-/-}$ mice hearts present with increased angiogenesis, as well as a decreased number along with an increased size variation of cardiomyocytes, compared to $Ptprz^{+/+}$ mice. The echocardiography analysis showed an overall decrease in LV function in $Ptprz^{-/-}$ mouse model (FS%: 32.51±2.01 vs 39.44±1.36, $p<0.05$), a LV dilation during diastole (LVEDD: 3.91±0.17 vs 3.35±0.09 mm, $p<0.0.5$) and an impaired systolic function (LVESD: 2.65±0.14 vs 2.03±0.06, $p<0.01$) compared to wild type littermates, respectively. Changes in ECM and signalling molecules were also observed.

Conclusions: These data suggest that the $Ptprz^{-/-}$ mice myocardium has a phenotype consistent with heart failure.

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PP38

TOXICITY STUDY OF GRAPHENE-COATED POLY(METHYL METHACRYLATE) MEMBRANES ON THE BRAIN CORTEX OF RATS

E. Tsianaka[1], E. Sereti[2], C. Papacharalambous[3], M. Ioannou[3], N. Pitsikas[2], A. Dimoulas[4], N. Sakellaridis[2], K. Fountas[1], K. Dimas[2]

[1] Department of Neurosurgery, University Hospital of Larissa, University of Thessaly, Larissa, Greece

[2] Department of Pharmacology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

[3] Department of Pathology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

[4] National Center for Scientific Research "Demokritos", Athens, Greece

Aim: Graphene is a relatively new material, which have being in great attention from the scientific community, because of its special characteristics and its potential use in medicine. Transparency, durability, elasticity and high conductivity make graphene a target material for applications in the field of neurosciences. The aim of this study was to determine the *in vivo* toxicity of graphene on the brain cortex by studying brain tissue reaction and the possible impairment of memory in a long term graphene exposure.

Materials-Methods: Graphene (Few Layers Graphene, FLG) produced by the Chemical Vapor Deposition and transferred on Poly(methyl methacrylate) (PMMA) membranes. FLG was sterilized by heating at 120 ? C under 1 bar pressure for 30 minutes. Male 3-month-old albino Wistar rats housed in Makrolon cages were used for the aims of this study. Material was placed on frontal brain cortex, after careful durotomy. Two groups of rats (3 rats each) were formed. Rats in group A underwent a sham surgery (control group). In Group B sterilized FLG/PMMA was implanted in the frontal brain cortex of the subjects. Three months after placement of FLG/PMMA spontaneous locomotor activity was assessed in an activity cage. Finally, brain tissue reaction was assessed three and a half months later after euthanasia of rats, removal and processing of their brains to paraffin blocks using a standard Hematoxylin and Eosin stain.

Results: Post-surgical period was normal for all studied animals, with no indications of toxicity or other pathological signs.Spontaneous locomotor activity test results indicated that graphene did not induce any change in horizontal or vertical motor activity of rats. Histologically, the examined tissue specimens regarding Group A showed no particular changes. Among specimens from the graphene group (Group B) only one sample showed slight mononuclear infiltration in the subarachnoid region.

Conclusion: In our *in vivo* study the application of FLG as a patch on the brain cortex gave encouraging results in regard to its safety. Extending studies, using larger cohort would be of great interest, in order safety of FLG for use in CNS, to be certified

PP39

ACTIVATED PLATELETS INDUCE THE FORMATION OF NEUTROPHIL EXTRACELLULAR TRAPS: THE EFFECT OF ADP RECEPTOR INHIBITION

I. Moschonas, S. Papadaki, A. Tselepis

Atherothrombosis Research Centre/Laboratory of Biochemistry, Department of Chemistry, University of Ioannina, Ioannina, Greece

Aim: We investigated the effect of activated platelets on NETs formation, as well as the possible inhibitory effect of ticagrelor, a specific ADP receptor antagonist.

Materials-Methods: Neutrophils were isolated from whole blood of apparently healthy volunteers by double-ficoll gradient, placed on poly-L-lysine coverslips and incubated for 1 h at 37°C, 5% CO_2. Autologous platelet-rich plasma (PRP) was prepared and the platelet count was adjusted to 2.5 X 10^8/mL. PRP was incubated with or without 1.25 μM ticagrelor for 5 min in an aggregometer under stirring and then activated with 20 μM ADP for 5 min. The platelet suspension was then transferred to neutrophils at a physiological cell number ratio and incubated for 3.5 h at 37°C, 5% CO_2. Alternatively, PRP was pre-mixed with neutrophils and incubated with or without 1.25 μM ticagrelor for 5 min, before activation *in situ* with 50 μM ADP for 3.5 h at 37°C, 5% CO_2. Neutrophils were then fixed, permeabilized and stained with anti-myeloperoxidase antibody and DAPI. The % NETs formation was evaluated by fluorescence microscopy.

Results: The suspension of platelets pre-activated with ADP in the aggregometer, increased NETosis by 106 ± 32%, whereas *in situ* platelet activation with ADP, increased NETosis by 63 ± 22% (p = 0.03 and p = 0.011, respectively, compared with resting platelets). Ticagrelor inhibited NETosis under both conditions, by 60 ± 10% and 77 ± 15%, respectively (p = 0.028 and p =0.012, compared with the respective activated samples).

Conclusions: ADP-activated platelets induce NETosis, which is inhibited by ticagrelor. Given the implication of neutrophils and NETs in various inflammatory conditions, the above results may represent a novel role of platelets, as well as the ADP receptor antagonists, beyond thrombosis. The clinical significance of the above results remains to be established.

PP40

DETECTING A POTENTIAL SIGNAL OF QUETIAPINE ABUSE IN THE FDA ADVERSE EVENTS REPORTING SYSTEM DATABASE

S. Siafis[1], D. Spachos[2], T. Siafi[1], G. Papazisis[1]

[1] Department of Clinical Pharmacology, School Of Medicine, Aristotle University of Thessaloniki, Greece

[2] Laboratory of Medical Physics, School of Medicine, Aristotle University of Thessaloniki, Greece

Introduction: Quetiapine is an atypical antipsychotic, which is frequently prescribed and off-label used. There is a growing literature of the potential misuse and abuse of quetiapine, which is also indicated by a recent analysis of the European Medicines Agency Adverse Drug Reactions' Database [1].

Methods: A case/non-case analysis was conducted in the FDA adverse events reporting system database (FAERS) using reports submitted from 2014 to 2017Q2. The analysis was performed using OpenVigil2.1-MedDRA, an open pharmacovigilance data extraction, mining and analysis tool of the FAERS database [2]. Cases were defined with the narrow scope of the SMQ 'Drug abuse and dependence'. All the other events were defined as non-cases. The reporting odds ratio (ROR) and its 95% confidence interval (CI) quantified the association between quetiapine with drug abuse events in comparison to all drugs in the database. Disproportional signals were detected when ROR - 95%CI was greater than one.

Results: From the 4.704.663 total number of reports, 57.086 included quetiapine. Drug abuse events were in 70.383 reports and 3.171 of them included quetiapine (5.55% of total quetiapine's reports). A disproportionality signal of drug abuse was detected for quetiapine with a ROR [95 % CI] of 4.01 [3.86-4.16]. Signals could be detected every year, except for the year 2007 (Figure).

Conclusion: Despite the inherent limitations of case/non-case studies, our results indicate the co-occurrence of drug abuse events with quetiapine.

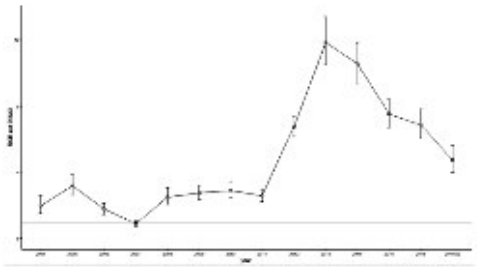

Figure: Temporal evolution of ROR for drug abuse and dependence of quetiapine. A safety signal was detected for every year, with the exception of 2007. The strongest evidence occurred in 2013.

PP41

DIFFERENTIAL RISK FOR TYPE II DIABETES AMONG ANTIDEPRESSANTS: A CASE/NON-CASE ANALYSIS OF THE FDA ADVERSE EVENTS REPORTING SYSTEM DATABASE

S.Siafis, G. Papazisis

Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Greece

Introduction: Recent evidence suggests the association between antidepressants and incident diabetes [1]. A case/non-case analysis of the FDA adverse events reporting system (FAERS) was conducted to assess the risk for diabetes of individual antidepressants.

Methods: Spontaneous reports submitted in FAERS between 2004 and 2017Q2 were analyzed. Data extraction was performed using OpenVigil2.1-MedDRA, an open data mining tool of the database [2]. Reports concerning the following antidepressants were extracted: amitriptyline, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, maprotriline, milnacipran, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, trazodone, trimipramine, venlafaxine. Data cleaning was performed to ascertain a minimum quality of data. Reports with concomitant antipsychotics, antidiabetics or combination of antidepressants were excluded. Cases were defined with the narrow scope of the SMQ 'Hyperglycemia/new-onset diabetes mellitus'. All other adverse events were defined as non-cases. The adjusted reporting odds ratio (aROR) for diabetes compared the proportion of diabetes with an individual antidepressant to the other antidepressants. aROR was adjusted to age, gender, reporting year and use of hyperglycemic drugs.

Results: After data cleaning, we found that 136028 reports concerned the 22 antidepressants and 1610 of them involved diabetes. Six antidepressants were associated with diabetes, with aROR [95% CI] of 2.01 [1.41-2.87] for nortriptyline, 1.97 [1.31-2.97] for doxepin, 1.82 [1.09-3.06] for imipramine, 1.47 [1.29-1.68] for sertraline, 1.33 [1.04-1.69] for mirtazapine, and 1.31 [1.09-1.59] for amitriptyline. Bupropion, citalopram, paroxetine, trazodone and desvenlafaxine were less frequently (aROR<1) associated with diabetes, while clomipramine, venlafaxine, duloxetine, fluoxetine, escitalopram, nefazodone, fluvoxamine and milnacipran were not associated with diabetes.

Conclusion: Most of the tricyclic antidepressants, mirtazapine and sertraline seem to be associated with diabetes in FAERS. Further clinical assessment is needed to validate this safety signal.

PP42

DOES ANTIOXIDANT TREATMENT EXERT ANXIOLYTIC EFFECTS?

M. Nussbaumer[1], L. Teplytska[1], M. Murphy[2], J. Asara[3], C. W. Turck[1], M. D. Filiou[4]

[1] Max Planck Institute of Psychiatry, Munich, Germany

[2] MRC Mitochondrial Biology Unit, University of Cambridge, UK

[3] Harvard Medical School, Boston, MA

[4] Department of Biological Applications and Technology, University of Ioannina, Greece and Max Planck Institute of Psychiatry, Munich, Germany

Aim: Although antioxidants are often provided as supplementary treatments for anxiety disorders, their anxiolytic effects have not been clearly demonstrated. To investigate the therapeutic potential of targeting oxidative stress, we tested whether the administration of different antioxidants exerts anxiolytic effects in high anxiety.

Materials and Methods: Groups of mice selectively bred for high anxiety received 3 different antioxidants through drinking water. We used the ubiquitous antioxidants carnosine (a free radical scavenger) and N-acetyl cysteine (precursor of the antioxidant glutathione) and the mitochondrial-targeted antioxidant MitoQ. We then assessed the effects of antioxidant treatment on anxiety-related and depression-like behavior by a battery of behavioral tests.

Results: The ubiquitous antioxidants carnosine and N-acetyl cysteine exerted no effect on the behavioral phenotype. On the contrary, administration of the mitochondrial-targeted antioxidant MitoQ resulted in decreased anxiety-related behavior in the dark-light box. This anxiolytic effect was specific for high anxiety mice and correlated with alterations in brain oxidative status.

Conclusions: Taken together, our data show that only antioxidant treatment which is selectively directed to mitochondria exerts anxiolytic effects. This points out towards a regulatory role of mitochondria in anxiety responses and highlights the potential of mitochondria as pharmacological targets for pertinent pathologies.

PP43

FLUMAZENIL BUT NOT BICUCULLINE COUNTERACT THE IMPAIRING EFFECTS OF ANESTHETIC KETAMINE ON RECOGNITION MEMORY IN RATS. EVIDENCE FOR GABAA-BENZODIAZEPINE RECEPTOR AGONISTIC PROPERTIES OF KETAMINE

A. Lafioniatis, V. Bermperian, N. Pitsikas

Department of Pharmacology, School of Medicine, University of Thessaly, Larissa, Greece

Background and Objectives: Experimental evidence indicates that anesthetic doses of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine impair memory abilities in rodents. The mechanism by which anesthetic ketamine produces its adverse behavioural effects is not yet clarified. In this context, it has been proposed that the effects of anesthetic ketamine on memory might be attributed to its agonistic properties on the γ-aminobutyric acid (GABA) type A receptor.

Thus, the present study was designed to investigated the ability of the benzodiazepine receptor antagonist flumazenil (1, 3, 6 mg/kg, i.p.) and the GABAA receptor antagonist bicuculline (0.5, 1.5, 3 mg/kg, i.p.) to counteract recognition memory deficits caused by anesthetic ketamine in rats.

Methods: For this purpose, the novel object recognition task (NORT) a behavioural paradigm assessing recognition memory abilities in rodents was used.

Results: Flumazenil (6 mg/kg, i.p.) counteracted anesthetic ketamine (100 mg/kg, i.p.)-induced performance deficits in the NORT. Conversely, bicuculline failed to attenuate the recognition memory deficits caused by anesthetic ketamine.

Conclusions: Our findings suggest that anesthetic ketamine's impairing action on recognition memory might depends on its agonistic properties on the benzodiazepine receptor.

PP44

HIGH- FREQUENCY OSCILLATIONS (HFOS) WITHIN INTERICTAL DISCHARGES (IEDS) OF HIPPOCAMPAL CA1 AREA IN VITRO: THEIR DEPENDENCE ON GENERATION MECHANISMS AND CHANGES WITH 4 HERBAL EXTRACTS

K. Kalogeropoulos[1], D. Kleidonas[1], A. Troganis[2], H. Stamatis[3], C. Psarropoulou[1]

[1] Human & Animal Physiology Laboratory, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece

[2] Environmental and Physicochemical Studies Laboratory, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece

[3] Biotechnology Laboratory, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece

Aim: Interictal discharges (IEDs) have been observed in epilepsy and other neuropathologies. High-frequency oscillations (HFOs) within them have been associated with normal (80-200Hz, Ripples, memory) and pathological (200-600Hz, Fast Ripples, epileptic foci, seizure onset) processes. We analyzed HFO features in 2 *in vitro* models of spontaneous IEDs with different generation mechanisms, as well as their changes following addition of 4 herbal extracts.

Materials-Methods: Extracellular recordings were performed on adult Sprague-Dawley-rat hippocampal slices. Perfusion with Mg^{2+}-free ACSF (NMDA-R activation, n=37 slices) or with 50μM 4-aminopyridine (4-AP, K^+ conductance inhibition, n=41) induced spontaneous IEDs, upon which the effects of herbal extracts of *Salvia officinalis*, *Olea europaea*, *Ilex paraguariensis*, και *Acorus calamus* were studied (all at a concentration of 0.1mg/mL). HFOs were visualized using an FIR filter, while their power spectra were calculated using a FFT (frequency domain measurements).

Results: Ripple ($p<0.0001$) and Fast Ripple ($p<0.0001$) durations differed significantly in the 2 models, in line to IED durations (4-AP: 0,06 ± 0,003 s, Mg^{2+}-free: 0,09 ± 0,006, $p<0.0001$). The model affected Ripple amplitude ($p=0.0006$), the delay between Ripple-IED onset ($p=0.008$) and between Fast Ripple-IED onset ($p=0.01$) and the peak power of Ripples (4-AP: 133,2 ± 5,2 Hz, Mg^{2+}-free: 147,7 ± 4,6 Hz, $p=0.04$). The extracts affected HFO characteristics differently in each medium. *Acorus calamus* reduced Ripple amplitude in 4-AP (-1,60±0.56 mV, n=5, $p=0.046$) and Ripple peak frequency in Mg^{2+}-free (-12.21±2.75 Hz, n=5, $p=0.007$). *Olea europaea* reduced Ripple amplitude in Mg^{2+}-free (1.71±0.60 mV, n=6, $p=0.0359$) while *Ilex paraguariensis* reduced the Fast Ripple-IED onset delay in 4-AP (-0.003±0.001s, n=5, $p=0.0115$).*Salvia officinalis* did not affect any HFO parameter. All four extracts altered frequency, duration and/or amplitude of IEDs depending on perfusion medium (previous research).

Conclusions: Statistically significant differences between Ripple and Fast Ripple features within IEDs in the two models suggest the importance of IED activation mechanisms for the characteristics of HFOs within them, and consequently for the synchronization tendencies of neuronal networks. The herbal extracts altered HFO characteristics, in variance to their pharmacological effects, indicating differences in the regulatory mechanisms of IEDs and the HFOs they contain.

PP45

HTTLPR POLYMORPHISM AND TREATMENT RESPONSE OF PSYCHOTIC PATIENTS IN A NATURALISTIC SETTING

A. Apostolidis[1], G. Papazisis[2], A. Sarrigiannidis[3], G. Garyfallos[3], A. Goulas[1]

[1] 1st Department of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] Laboratoty of Clinical Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[3] 2nd Department of Psychiatry, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

Introduction- Aim: The function of the serotonin transporter (5-HTT, SERT) is essential for the regulation of serotonin (5-HT) signaling, which affects many aspects of mood and behavior. HTTLPR (rs4795541) is an insertion – deletion polymorphism, in a repetitive element located approximately 1.5 kb upstream from the SERT gene, *SLC6A4*. HTTLPR and its accompanying SNP, rs25531, have been associated in the past with response to antidepressant drugs, substance use disorder, stress response, and pain perception, but there is also some evidence that it may be related to schizophrenia as well. The aim of this study was to examine the association of HTTLPR with response to treatment with antipsychotic drugs in a naturalistic setting.

Materials and Methods: Ninety-one Greek patients suffering from schizophrenia and other psychotic disorders were included in this study. Genotyping of rs4795541 and rs25531 was accomplished with PCR, and RLFP-PCR, respectively. The genotype distribution of the combination (tri-allelic) polymorphism was associated with the positive and negative syndrome scale at presentation ($PANSS_{base}$) – a measure of psychotic symptom severity, its difference following four weeks of treatment ($PANSS_{dif}$) – a measure of response to treatment, and the average daily administration of antipsychotic drugs, normalized to chlorpromazine equivalents (CPZ_{eq}).

Results: We have detected a trend of the L_AL_A genotype to associate with reduced CPZ_{eqs} and with a lower score on the negative symptom PANSS subscale. Otherwise, a statistically significant improvement of general psychopathology symptoms was detected in males as compared to females, as was an inverse correlation of $PANSS_{base}$ to the age of onset of the disease.

Conclusions: The 5-HTTLPR polymorphism does not appear to be a strong determinant of either the severity of psychotic symptoms or the response to antipsychotic drugs, under the conditions of this study.

PP46

AROMATASE INHIBITION DIFFERENTIALLY IMPACTS HIPPOCAMPAL METABOLISM IN MALE AND FEMALE YOUNG AND AGED RATS

M.D. Filiou[1,2], **N. Kokras** [3,4], **M. Koronaiou** [3], **C.W. Turck** [2], **C. Dalla**[3]

[1]*Department of Biological Applications and Technology, School of Health Sciences, University of Ioannina, Ioannina, Greece*

[2]*Max Planck Institute of Psychiatry, Munich, Germany*

[3]*Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece*

[4]*First Department of Psychiatry, Eginition Hospital, National and Kapodistrian University of Athens, Athens, Greece*

Introduction-Aim: Aromatase inhibitors block the conversion of androgens to estrogens and are used to treat breast cancer in menopausal women. In addition, they have psychotropic activities due to estrogen inhibition in the brain. Recent studies have shown that subacute treatment with the aromatase inhibitor letrozole exerts an antidepressant effect in cycling female rats and sustained aromatase inhibition results in neurotransmitter level differences between male and female brains.

Methods: In the present study, adult and aged male and adult cycling and aged female rats in senescence received subacute letrozole or vehicle treatments consisting of 3 i.p. injections within 24 hours. To assess the effects of letrozole administration, we compared the metabolite profiles in the hippocampus of letrozole- or vehicle-treated male and female young and aged rats. We used a targeted metabolomics platform measuring up to 300 metabolites the levels by liquid chromatography tandem mass spectrometry. Data were analyzed by MetaboAnalyst.

Results: Letrozole administration resulted in significant metabolite level alterations in young females. SAM analysis revealed a group of 10 significant metabolite changes (FDR<0.05) between letrozole- and vehicle-treated young female rats. These metabolites are involved in betaine and amino acid metabolism with reduced levels following letrozole treatment. Intriguingly, the observed metabolite changes were blunted in older females. No significant metabolite level alterations were found in males irrespective of age. ***Conclusions:*** These data indicate a sex- and age-dependent effect of letrozole treatment which is likely dependent on the estrogen status of female rats. The results are important for women treated with aromatase inhibitors.

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PP47

PLANTS IN ALZHEIMER'S DISEASE

A. Kotsiou[1,2], A. Bogas Manouselis[3], C. Tesseromatis[2]

[1] *"Aretaieio" University Hospital of Athens, Athens, Greece*

[2] *Pharmacology Department, Faculty of Medicine, School of Health Sciences, University of Athens, Athens, Greece*

[3] *Faculty of Medicine, School of Health Sciences, University of Athens, Athens, Greece*

Aim : To investigate the potential therapeutic effect of herbal medicines on Alzheimer's disease. Current available therapies mediate symptoms without modifying this still incurable disease progression, associated with β-amyloid plaques deposit in the brain.

There are a few approved medications, acetylcholinesterase inhibitors (tacrine, rivastigmine, galantamine, donepezil) and NMDA receptor antagonist : memantine and many under clinical trials. Galantamine and rivastigmine are plant – derived agents.

Method: Current literature, on medicinal plants' potential to inhibit both β-amyloid protein deposit in the brain and acetylcholinesterase activity, in laboratory studies and in clinical trials, is reviewed.

Results: Hundreds of plants species have been tested and a large number of them are documented with the desired properties.

In the present review we focus mainly on species endemic to Greece and on some other widely known in folk medicine such as : Bacopa monnieri , *Brassica alba, Camellia sinensis,* Celastrus paniculatus, Centella asiatica, *Cinchona officinalis,* Cissampelos pareira*, Citrus aurantifolia,* Commiphora whighitti, Convolvulus pluricaulis, Coriandrum sativum, Crocus sativus, Curcuma longa , Emblica officinalis, Evolvulus alsinoides, Ficus carica, Ficus racemosa, *Ficus religiosa,* Galanthus Caucasius, Galanthus ikariae, Ginkgo biloba, Glycyrrhiza glabra, *Humulus lupulus*, *Humulus japonicum,* Hypericum perforatum, Ilex paraguariensis, Lepidium meyenii, Magnolia officinalis, Mellisa officinalis, Moringa oleifera, Nardostachys jatamansi, Olea europaea, Panax ginseng, *Piper nigrum, Pistacia vera,* Punica granatum*, Rheum officinale, Rosa damascena, Rosmarinus officinalis*, Salvia officinalis, Theobroma cacao, Withania somnifera.

Conclusion : Given the limited efficacy of the few available licensed medications and their side-effects (nausea, vomiting), plants should be considered as promising sources for new directions in drug development *for the treatment of Alzheimer's disease. With* drug–drug interaction being their only potential side effect, plants' extracts are the safest agents with proven clinical efficacy , according to the concept of 'evidence based medicine'.

PP48

ROLE OF OLEUROPEIN-INDUCED PPARA ACTIVATION IN NEURAL PLASTICITY

F. Malliou[1], C. E. Andriopoulou[1], T. Michaelidis[2], A. Katsogridaki[1], F. Kanellos [1], L. Skaltsounis[3], M. Darsinou[1], M. Konstandi[1]

[1] Laboratory of Pharmacology, Medical School, University of Ioannina, Ioannina, Greece

[2] Department of Biological Applications & Technology, School of Health Sciences, University of Ioannina

[3] National & Kapodistrian University of Athens, Athens, Greece

The main constituent of olive, oleuropein, is isolated from the olive leaves and oil. The oleuropein-induced activation of the nuclear transcription factor, peroxisome proliferator-activated receptor alpha (PPARα), is associated with several beneficial effects, including those on lipid homeostasis and cardiovascular function. PPARα is expressed in neurons and astrocytes and its activation provides neuroprotection against noxious biological reactions including ischemia. The present study has focused on the role of PPARα activation in neural plasticity. For this purpose, adult male SV129 wild type mice were treated with oleuropein for 6 weeks (100mg/day in 3g food pellet + 0,3g sucrose). P*para*-null mice followed a similar treatment protocol. It was observed that long term treatment with oleuropein significantly induced various neural plasticity-related neurotrophins and their receptors including the brain-derived neurotrophic factor (BDNF) and its receptor TrkB in the prefrontal cortex (PFC), potentially by activating MAP kinases. No similar effects were observed in the hippocampus. It is of interest to note that the oleuropein-induced effects on these critical neural plasticity factors in the PFC are mediated by PPARα, because no alterations in these factors were observed in P*para*-null mice. In conclusion, the findings of this study suggest that drugs acting as PPARα agonists could improve neural plasticity and subsequently, cognitive functions and therefore, they could be beneficial in preventing or delaying the progression of neurodegenerative disorders. Further studies though, should be designed employing *in vitro* and *in vivo* models and behavioral tests to thorough investigate this hypothesis.

PP49

SMALL MOLECULES TARGETING CRF1R DISPLAY ANTAGONISTIC PROPERTIES

V. Karageorgos [1], M.-T. Matsoukas [2], S. Sakellaris [1], M. Pardalos [1], A. Konstantinou[1], P. Kapsali [1], B. Kuppast [4], M. Teleb [4], A. Margioris [1], H. Fahmy [4], G. Liapakis[1]

[1] Medical School, University Of Crete, Crete, Greece

[2] University Of Patras, Patras, Greece

[4] College Of Pharmacy, South Dakota State University, USA

Aims: Corticotropin releasing factor (CRF), a 41 amino acid peptide, plays a key role in body response to stress by interacting predominantly with its type 1 receptor (CRF1R) and regulating the activity of hypothalamic-pituitary-adrenal axis and many brain regions. Malfunctioning of CRF/CRF1R-neuronal circuits is closely associated with the appearance of anxiety and depression. Many CRF1R-selective antagonists display antidepressant and anxiolytic properties in preclinical studies. However, none of the CRF1R antagonists is available for clinical use. This study aims in synthesizing new small non-peptide substituted pyrimidines and determine their ability to antagonize the CRF-related peptide, sauvagine.

Materials and methods: To determine the pharmacological properties of our novel small analogues, we have used various experimental approaches, such as cell culture, cell signaling experiments and molecular modeling.

Results: Analogues having a methyl group at position 2, a 2,4,6-trimethylphenyl group at position 4, a methyl or ethyl group in the alkythiol group at position 5 and a N,Nbis(methoxyethyl)amino group or N-cyclopropyl-N-methylpropylamino at position 6 bound to CRF1R. To test the antagonistic properties of these non-peptide analogues we determined their ability to inhibit the stimulation of adenylyl cyclase by 10 nM sauvagine in HEK 293 cells expressing CRF1R. The results of these experiments showed that our non-peptide molecules are potent antagonists. Molecular modeling data based on the crystal structure of CRF1R were constructed and demonstrated the contact sites of these small molecules in receptor.

Conclusions: Based on our results we conclude that small substituted pyrimidines having a methyl group at position 2, a 2,4,6-trimethylphenyl group at position 4, a methyl or ethyl group in the alkythiol group at position 5 and a N,Nbis(methoxyethyl)amino group or N-cyclopropyl-N-methylpropylamino at position 6 are potent CRF1R antagonists. This study will provide the basis for the receptor-based design of novel non-peptide CRF1R antagonists with antidepressant and anxiolytic properties.

PP50

THE ROLE OF LITHIUM IN MITOCHONDRIAL HOMEOSTASIS IN CAENORHABDITIS ELEGANS

E. Asimaki[1], K. Palikaras[1], N. Tavernarakis[1,2]

[1] Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Heraklion, Crete, Greece

[2] Faculty of Medicine, School of Health Sciences, University of Crete, Heraklion, Crete, Greece

Mitochondria are highly dynamic, energy-generating organelles in eukaryotic cells and play an essential role in fundamental cellular processes. Mitochondrial function impinges on several signaling pathways modulating cellular metabolism, cell survival and organismal healthspan. Mitochondrial damage and aberrant accumulation of defective organelles in various cell types are shared hallmarks of many pathological conditions. Thus, maintenance of cellular homeostasis necessitates a tight regulation of mitochondrial quality control mechanisms to sustain mitochondrial function. Lithium supplementation have been used to treat several neurodegenerative diseases, including bipolar disorder, depression and schizophrenia among others. However, little is known about the mechanism of its action and the interplay with mitochondria quality control pathways. To address these questions, we use the nematode *Caenorhabditis elegans* to investigate the role of lithium in the preservation of energy metabolism. We developed an imaging system to monitor *in vivo* mitochondrial selective autophagy in neurons. Neuronal mitophagy is not induced in response to lithium treatment. Interestingly, lithium supplementation enhances mitochondrial activity and increases mitochondrial number in neurons. Our results indicate that lithium triggers mitochondrial biogenesis in neuronal cells and contributes to promote mitochondrial homeostasis and survival.

PP51

AMP-ACTIVATED KINASE (AMPK) IN CARDIOVASCULAR AND METABOLIC DISEASE: PHYSIOLOGY, PHARMACOLOGY AND WHAT LIES BENEATH

E. P. Daskalopoulos, C. Dufeys, F. Mailleux, R. Gélinas, S. Lepropre, M. Ange, D. Castanares-Zapatero, L. Bertrand, C. Beauloye, S. Horman

Ptle de Recherche Cardiovasculaire (CARD), Institut de Recherche Expırimentale et Clinique (IREC), Universitı catholique de Louvain (UCL), Brussels, Belgium

The AMP-activated protein kinase (AMPK) is a ubiquitously expressed cellular energy sensor which maintains energy homoeostasis under physiologic and stress conditions. Its role in coordinating anabolic and catabolic activities of the cardiomyocyte in the adaptive response to energy stress (e.g. following ischemia) is essential for cell survival. Furthermore, a considerable amount of evidence has demonstrated that the beneficial actions of AMPK in the myocardium extend well beyond its metabolic roles. Here, we will provide an in-depth overview of the physiologic roles of the AMPK signaling pathway and discuss in detail about novel findings related to its protective effects on the cardiomyocytes (targeting hypertrophy), the cardiac fibroblasts (targeting fibrosis), the endothelial cells (targeting sepsis-induced cardiac dysfunction) and platelets (targeting thrombosis). Lastly, we will highlight the published literature relating to the already established and novel agonists / antagonists that can form part of the pharmacotherapeutic arsenal against a wide range of cardiovascular pathologies.

PP52

COMPARING SITAGLIPTIN TO METFORMIN IN AN EXPERIMENTAL MODEL OF DIABETIC NEPHROPATHY. THE EFFECTS OF SITAGLIPTIN ON THE KIDNEYS

I. Tsavdaridis[1], D. Papadimitriou[1], G. Karayannopoulou [2], A. Foka-Karagiannopoulou [2], M. Mironidou Tzouveleki[1]

[1] A' Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2] Laboratory of General Pathology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

Dipeptidyl peptidase- IV inhibitors have been used for 10 years as treatment for diabetes mellitus (DM). DM has been directly correlated with micro and macrovascular complications as well as with atherosclerotic cardiovascular conditions and nephropathy. However, research has not been focusing on the effects of these treatment on DM complications. In this study we aim to explore the effects of sitagliptin on diabetic nephropathy using an experimental animal model while comparing it with metformin. 36 male BKS.Cg- + Leprdb / + Lepr + / OlaHsd mice, 8 weeks old, were evenly separated into four groups. For 12 weeks group D and L received a high (200mg/Kgr/day) and low (10mg/kgr/day) dosage of sitagliptin respectively while group M received a of 150mg/Kgr/day metformin. Group N did not receive any treatment. Biochemical tests on urinary and blood samples of each animal as well as histopathological examination for specific lesions of the kidneys were performed at the end of the experimental study. All data were analyzed using the IBM SPSS Statistcs program Version 24. High sitagliptin dosage was found to significantly reduce serum glucose (P: 0,0001) as well as in urinary creatinine (P: 0,0001), microalbumin (P: 0,013) and Albumin Creatinine Ratio (P: 0,0001) when compared to the control group. Moreover, mesangial matrix expansion (P: 0,0001), thickening of the basement membrane (P:0,020) and vascular pole hyalinosis (P: 0,042) were significantly reduced in group D compared to control group. However, there was no statically significant differences between the groups receiving high dosage sitagliptin and metformin. Sitagliptin in high doses appears to improve the biochemical parameters regarding kidney function and acts beneficially by reducing the extent of histopathological damage caused by DM in the kidney. However these results seem to be caused by the reduced serum glucose and not by a direct effect on the kidneys since no differences were observed by the use of metformin. Those positive effects should be re-evaluated on a clinical level with large scale multicenter studies in order to be able to fuuly comprehend them and take advantage of them in the everyday clinical practice

PP53

AMPLIFIED STABILITY AND THERAPEUTIC EFFICACY OF TEMOZOLOMIDE THROUGH INCORPORATION INTO A SUPRAMOLECULAR CARRIER

A. Tsiailanis[1], A. W. J. Renziehausen[2], C. Hatzigiannis[1], E. Stilos[1], R. Perryman[2], N. Syed[3], A. G. Tzakos[1]

[1] Section Of Organic Chemistry And Biochemistry, Department Of Chemistry, University Of Ioannina, Ioannina, Greece

[2] John Fulcher Neuro-Oncology Laboratory, Imperial College London, Hammersmith Hospital, London, UK

[3] John Fulcher Neuro-Oncology Laboratory, Imperial College London, Hammersmith Hospital, London, UK

Aim: Temozolomide (TMZ) is an oral alkylating agent with established therapeutic efficacy against a variety of solid tumours and it is the first in line treatment for glioblastoma (GBM). TMZ is able to cross the blood brain barrier (BBB) due to its small size and lipophilic nature. Despite its encouraging activity against brain tumours, TMZ has numerous unfavorable characteristics that greatly limit its efficacy and clinical use. These include its poor aqueous solubility and limited stability. TMZ is stable at acidic pH of the stomach, however, under slightly alkaline conditions, it is rapidly hydrolyzed to the active metabolite MTIC. The therapeutic potency of MTIC is limited due to its poor penetration of the BBB and limited cellular uptake. Therefore, to prolong the lifetime of TMZ in order to achieve greater BBB penetration, as well as improve its solubility, we synthesized a complex of TMZ with a supramolecular carrier.

Material and Methods: ^{1}H NMR spectroscopy and UV-Vis spectroscopy were used to demonstrate the stability of TMZ in the complex. Also,UHPLC-MS/MS plasma stability experiments were conducted. The therapeutic efficacy of the TMZ complex was compared to that of free TMZ in different GBM cell lines. Finally *in vivo* experiments were conducted.

Results: ^{1}H NMR spectroscopy and UV-Vis spectroscopy revealed a significantly increased half-life of the complexed TMZ by 6 hours compared to free TMZ when incubated in phosphate buffer (pH*=7) at 37°C. The *in vitro* experiments illustrated efficacy of the TMZ complex with respect to free TMZ in GBM cell lines (LN229, U87, 8MG), patient derived primary GBM cells (TB77, GBM59, GBM31), metastatic melanoma cells (SKMEL 23) and medulloblastoma cell lines (UW228,). Preliminary *in vivo* evaluation show promising results and studies are ongoing to evaluate the therapeutic efficacy of the TMZ-complex compared to unbound TMZ.

Conclusions: The complexed TMZ illustrated enhanced stability in contrast to free TMZ. In all cancer cell lines, the complex was much more effective at reducing cancer cell growth than TMZ alone. Particularly striking are the results for UW228 and the primary GBM cells as these are normally highly resistant to TMZ.

PP54

MECHANISTIC ASPECTS OF THE INTERACTION OF PLEIOTROPHIN WITH NUCLEOLIN

E. Choleva[1], M. Koutsioumpa[2], C. Polytarchou[3], D.Iliopoulos[2], E. Pantazaka[1], Md Sanaullah Sajib[4], C. M. Mikelis[4], E. Papadimitriou[1]

[1] *Department of Pharmacy, University of Patras, Patras, Greece*
[2] *David Geffen School of Medicine, University of California At Los Angeles, USA*
[3] *School of Science and Technology, Nottingham Trent University, Nottingham, England*
[4] *School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, Tx, USA*

Aim: Angiogenesis, the formation of new blood vessels, plays an essential role in normal growth and development, as well as in tumor growth and metastasis. Pleiotrophin (PTN) is a secreted heparin-binding growth factor that through its receptor protein tyrosine phosphatase beta/zeta (RPTPβ/ζ), $\alpha_v\beta_3$ integrin and cell surface nucleolin (NCL) has a significant regulatory role on angiogenesis and cancer. In the present work, differentially tagged wild-type and mutant PTN and NCL plasmid constructs have been used to investigate the domains of both molecules involved in their interaction and signaling.

Material and Methods: pEGFP-c1 plasmid constructs carrying wild-type NCL (GFP-NCL) or NCL domains 1-275 (M1 corresponding to the NH_2-domain of NCL), 308-645 (M2, corresponding to the central RNA binding domainof NCL) or 308-707 (M3 corresponding to both the central and the COOH-terminal part of NCL, the latter being rich in glycine and arginine residues) were made. pcDNA3-c-Flag plasmid constructs carrying wild-type PTN or PTN domain 9-59 were also made. Human glioblastoma U87MG cells were transiently transfected to over-express NCL or PTN constructs and the interaction of the expressed NCL domains with PTN was tested by a combination of immunoprecipitation and Western blot analyses.

Results: PTN interacts through its amino-terminal domain with both M2 and M3 but not M1 NCL domains. A peptide that is known to bind to the COOH-domain of NCL does not inhibit PTN-NCL binding, suggesting the RNA-binding domain of NCL is involved in PTN binding.

Conclusions: These data suggest that the amino-terminal and most likely the carboxy-terminal domains of NCL are not involved in interactions with PTN, while the RNA binding domain seems to have a significant, previously unidentified role. PTN binds to NCL through its amino-terminal domain and this will be exploited for the design of bioactive molecules to inhibit PTN activities related to NCL binding and signaling.

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PP55

TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 (TRPA1) CHANNELS ON THE SCIATIC NERVE CONDRIBUTE TO THE DEVELOPMENT OF NEUROPATHIC PAIN

A. Tsobou, K. Karali, S. Fiaska, M. Gerou, C. Labrakakis

Department of Biological Applications and Technology, School of Health Sciences, University of Ioannina, Ioannina, Greece

Aim: Neuropathic pain is a persisting condition arising from damage in the somatosensory system. The prevalence of neuropathic pain is high, but the treatment options are limited. Nerve entrapments are a common cause for neuropathic pain (spinal canal stenosis, carpal tunnel syndrome), however the cellular and molecular mechanisms involved in the pathogenesis are not well studied. Here we postulate that mechanical pressure on the nerves during the entrapment might activate mechanosensitive ion channels on the axonal membranes which could cause accumulation of Ca^{2+} in the axoplasma and lead to sensitization and degeneration of axons. TRPA1, are Ca^{2+}-permeable ion channels and are considered as multimodal sensory receptors sensitive to a wide range of stimuli. These include environmental irritant chemicals like mustard oil and allicin, as well as endogenous products of ROS mediated oxidation and lipid metabolites. In addition TRPA1 are also sensitive to mechanical pressure and cold temperatures. They are expressed in subpopulations of primary afferent neurons involved in nociception. Thus TRPA1 might be involved in the development of neuropathic pain.

Methods and Results: Using electrophysiological recordings of compound action potentials in isolated rat sciatic nerves and TRPA1 agonists and antagonists, we provide evidence of their functional expression on peripheral sensory axons. We then use the TRPA1 agonist allylisothiocyanate (AITC) on the sciatic nerve *in vivo*, and find that a single application of AITC can cause the development of mechanical hypersensitivity several days later. This indicates that activation of TRPA1 may underlie the development of neuropathic pain. In additional experiments, using fluorescence and isolated sciatic nerves, we explored the involvement of axonal mitochondria and metabolic activity in the AITC induced neuropathy.

Conclusions: Our results provide a strong indication that chronic mechanical and chemical stimuli may involve endogenous mechanisms (i.e. mechanosensitive and chemosensitive ion channels) in the generation of neuropathy and nociceptive hypersensitivity.

PP56

THE E3, E4 UBIQUITIN LISAGE UBE4B IN HUMAN CANCER

N. Antoniou[1], N. Lagopati[1], T. Loutas[2], N. Margetis[1], T. Mariolis-Sapsakos[2], G.V. Gorgoulis[1], Y. Shiloh[3], A. Kotsinas[1]

[1] Lab Histology-Embryology, Medical School, National and Kapodistrian University of Athens, Greece

[2] Anatomy and Histology Laboratory, Nursing School, National and Kapodistrian University of Athens, Greece

[3] The David and Inez Myers Laboratory for Cancer Research, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, George S. Wise Faculty of Life sciences, Tel Aviv University, Tel Aviv, Israel

Post-translational modifications (PTMs) enable cells to react dynamically to intracellular or environmental changes, caused by stress factors, growth stimuli or differentiation signals. Among them, ubiquitin (Ub) PTMs have a broad role in cell cycle regulation. Interestingly, the enzymes that catalyze the labeling of various proteins with ubiquitin moieties for proteasomal degradation actively participate in DNA Damage Response. UBE4B is a newly identified member, belonging to E3 ubiquitin ligases, namely E4 containing a U-BOX catalytic domain. Recent data suggest an interplay between UBE4B and p53, including its homologs (p63, p73), in tumor development. The main aims of this study are to: i) assess UBE4B expression in human cancer datasets; 2) correlate expression of UBE4B with p53; and iii) explore the effect of DNA Damage on UBE4B protein levels. Our results indicate that UBE4B protein is overexpressed in human lung cancer and correlates with p53 mutational status. Also, UBE4B is overexpressed in pre-cancerous and cancerous lesions of human colon tissues, often associated with p53 expression. UBE4B overexpression was not due to gene amplification, but mainly through transcriptional activation or post-translational stabilization. Preliminary *in vitro* data suggest that DNA damage increases UBE4B expression levels, leading to chromatin loading and foci formation. UBE4B may also possibly be involved in p53 protein levels regulation. Overall, our data suggest a potential role for UBE4B in cancer development from the earliest stages, possibly through interplay with p53. Nevertheless, further studies are needed to elucidate the exact mechanistic basis and its prospective therapeutic exploitation.

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Όλες οι Προφορικές και Αναρτημένες ανακοινώσεις θα πρέπει να προετοιμαστούν στην **αγγλική** γλώσσα.

ΠΡΟΦΟΡΙΚΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ

Η παρουσία των Προφορικών Ανακοινώσεων θα γίνει σύμφωνα με το Επιστημονικό Πρόγραμμα. Η διάρκεια των Προφορικών Ανακοινώσεων θα είναι **8 λεπτά** συμπεριλαμβανομένης και της συζήτησης.

ΑΝΑΡΤΗΜΕΝΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ (POSTERS)

Πρόγραμμα Ανάρτησης Ανακοινώσεων

Σάββατο 26/05/2018	08:30 - 10:00	**Ανάρτηση Poster** - Session A', Foyer Συνεδριακής Αίθουσας
	19:30 - 20:00	**Απόσυρση Poster**- Session A'
Κυριακή 27/05/2018	08:30 - 10:00	**Ανάρτηση Poster** - Session B', Foyer Συνεδριακής Αίθουσας
	19:30 - 20:00	**Απόσυρση Poster** - Session B'

Σημείωση: *Υλικό για την ανάρτηση των Ανακοινώσεων θα βρίσκεται στη διάθεσή σας τόσο στο χώρο ανάρτησης όσο και στη Γραμματεία του Συνεδρίου*

ΟΜΙΛΙΕΣ/ΠΑΡΟΥΣΙΑΣΕΙΣ - ΤΕΧΝΙΚΗ ΓΡΑΜΜΑΤΕΙΑ

Δήλωση Συμφερόντων

Σύμφωνα με την εγκύκλιο του ΕΟΦ, όλοι οι ομιλητές που συμμετέχουν σε επιστημονικές εκδηλώσεις αντί της έγγραφης δήλωσης συμφερόντων θα πρέπει να αναφέρονται στην ομιλία τους, στη δεύτερη διαφάνεια της παρουσίασής τους (μετά ακριβώς από την πρώτη διαφάνεια η οποία αναφέρει τον τίτλο της ομιλίας τους), σε οποιαδήποτε σύγκρουση συμφερόντων αναφορικά με τους χορηγούς του Σεμιναρίου.

Διάρκεια Ομιλιών

Ο χρόνος των ομιλιών θα πρέπει να τηρείται αυστηρά τόσο από τους ομιλητές όσο και από τους προεδρεύοντες και συντονιστές έτσι ώστε να μην στερείται από τους επόμενους ομιλητές και να διασφαλίζεται η ροή του προγράμματος.

Παράδοση Ομιλιών/Παρουσιάσεων

Όλοι όσοι συμμετέχουν με ομιλία - παρουσίαση παρακαλούνται να παραδώσουν το υλικό της παρουσίασης τους (σε PowerPoint με USB/CD/DVD) στην Τεχνική Γραμματεία που θα λειτουργεί εντός της συνεδριακής αίθουσας τουλάχιστον 1 ώρα πριν την έναρξη της επιστημονικής ενότητας (προς επιβεβαίωση της λειτουργίας του ή/και προς επιδιόρθωση τεχνικών προβλημάτων).

Καινοτομία.
Φανταστείτε τις δυνατότητες.

Στη Janssen, κάνουμε μεγάλα όνειρα.

Φανταζόμαστε μια εποχή όπου οι ασθένειες θα θεραπεύονται πριν καν εκδηλωθούν. Μια εποχή που όσοι έχουν ανάγκη, θα έχουν πρόσβαση σε φάρμακα που σώζουν ζωές, όπου κι αν βρίσκονται.
Μια εποχή που οι θεραπείες θα είναι τόσο απλές, που οι άνθρωποι θα περνούν περισσότερο χρόνο κάνοντας αυτά που αγαπούν.

Πρόκειται για μια εντελώς καινοτόμο προσέγγιση στην αντιμετώπιση, πρόληψη και αναστολή των ασθενειών, τώρα και στο μέλλον.

Συνεργαζόμαστε με τους καλύτερους ερευνητές από κάθε τομέα, μεταφράζουμε τα μεγάλα οράματα σε λύσεις που αλλάζουν τα δεδομένα. Επειδή οι ασθενείς περιμένουν.

Είμαστε η Janssen. Συνεργαζόμαστε με όλον τον κόσμο για την υγεία όλων.

Μάθετε περισσότερα στην ιστοσελίδα http://www.janssen.com/greece/

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Στην εικόνα απεικονίζονται μοντέλα που χρησιμοποιούνται για εικαστικούς λόγους μόνο.

PHGR/CMN/0617/0001

Τόπος Διεξαγωγής
Ξενοδοχείο Grand Serai, Ιωάννινα

Ημερομηνίες Διεξαγωγής

Επιστημονικό Πρόγραμμα

Παρασκευή 25/05/2018, 10:00-20:40, Ξενοδοχείο Grand Serai
Σάββατο 26/05/2018, 09:00-19:20, Ξενοδοχείο Grand Serai
Κυριακή 27/05/2018, 09:30-19:15, Ξενοδοχείο Grand Serai

Προφορικές Ανακοινώσεις
Σάββατο 26/05/2018, 13:45-15:00
Κυριακή 27/05/2018, 13:45-15:15

Αναρτημένες Ανακοινώσεις
Σάββατο 26/05/2018, 11:15-11:45, Foyer Συνεδριακής Αίθουσας
Κυριακή 27/05/2018, 11:00-11:30, Foyer Συνεδριακής Αίθουσας

Επίσημη Γλώσσα
Επίσημη γλώσσα του Συνεδρίου είναι η Ελληνική και η Αγγλική. Οι παρουσιάσεις των ξένων προσκεκλημένων ομιλητών θα πραγματοποιηθούν στα Αγγλικά χωρίς ταυτόχρονη διερμηνεία στα Ελληνικά.

Εγγραφές

Κόστος εγγραφής:

[1]Μέλη Εταιρείας	20 ευρώ
[1]Μη Μέλη Εταιρείας	30 ευρώ
[2]Φοιτητές	Δωρεάν

[1]***Η εγγραφή περιλαμβάνει:***
- *Παρακολούθηση του επιστημονικού προγράμματος*
- *Επίσκεψη στον Εκθεσιακό Χώρο*
- *Συμμετοχή σε Διαλείμματα Καφέ/ Γεύμα/Δεξίωση Υποδοχής*
- *Συνεδριακό Υλικό (έντυπο υλικό του Συνεδρίου, ταυτότητα εισόδου)*
- *Πιστοποιητικό παρακολούθησης*

[2]***Η εγγραφή περιλαμβάνει:***
- *Παρακολούθηση του επιστημονικού προγράμματος*
- *Επίσκεψη στον Εκθεσιακό Χώρο*
- *Πιστοποιητικό παρακολούθησης*

Κονκάρδες

Με την παραλαβή του υλικού όλοι οι συμμετέχοντες θα λάβουν την ονομαστική τους κονκάρδα που θα φέρει ένα μοναδικό barcode. Οι κονκάρδες με το barcode θα πρέπει να σαρώνονται στο ειδικό μηχάνημα πριν από την είσοδο και κατά την έξοδο από τη συνεδριακή αίθουσα, για να καταγράφονται οι ώρες παρακολούθησης.

Σύμφωνα με την εγκύκλιο του ΕΟΦ, είναι υποχρεωτική η παρακολούθηση **ποσοστού 60% επί των συνολικών ωρών του επιστημονικού προγράμματος** για την παραλαβή της Βεβαίωσης Παρακολούθησης. Η επίδειξη της κονκάρδας θα είναι απαραίτητη καθ' όλη τη διάρκεια του Συνεδρίου (καθώς και η παράδοση της για την παραλαβή της Βεβαίωσης Παρακολούθησης).

Οι κονκάρδες με το barcode:
Είναι μοναδικές και δεν μπορούν να αντικατασταθούν.
Στην καταμέτρηση των ωρών δεν προσμετρούνται τα διαλείμματα και τα δορυφορικά συμπόσια.

Βεβαιώσεις Παρακολούθησης

Οι Βεβαιώσεις Παρακολούθησης θα δοθούν στους συμμετέχοντες από την Γραμματεία με το πέρας του Συνεδρίου ΜΟΝΟ κατόπιν παράδοσης της κονκάρδας και του συμπληρωμένου Ερωτηματολογίου Αξιολόγησης.

Ερωτηματολόγιο Αξιολόγησης

Όλοι οι συμμετέχοντες θα κληθούν να συμπληρώσουν (ανώνυμα) και να παραδώσουν στη Γραμματεία με το πέρας του Συνεδρίου, το σχετικό Ερωτηματολόγιο Αξιολόγησης (που βρίσκεται στο έντυπο υλικό του Συνεδρίου).

Τεχνική Γραμματεία

Όλοι όσοι συμμετέχουν με ομιλία – παρουσίαση παρακαλούνται να παραδώσουν το υλικό της παρουσίασης τους (σε PowerPoint με USB/CD/DVD) στην Τεχνική Γραμματεία που θα λειτουργεί εντός της συνεδριακής αίθουσας τουλάχιστον 1 ώρα πριν την έναρξη της επιστημονικής ενότητας (προς επιβεβαίωση της λειτουργίας του ή/και προς επιδιόρθωση τεχνικών προβλημάτων).

ΟΡΓΑΝΩΤΙΚΟ – ΣΥΝΤΟΝΙΣΤΙΚΟ ΓΡΑΦΕΙΟ

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ΕΥΧΑΡΙΣΤΙΕΣ

Η **Οργανωτική Επιτροπή** του Συνεδρίου και το **Διοικητικό Συμβούλιο της Ελληνικής Βασικής και Κλινικής Φαρμακολογίας** ευχαριστούν θερμά για την υποστήριξή τους στην υλοποίηση του συνεδρίου

Την Περιφέρεια Ηπείρου

Τον Δήμο Ιωαννιτών

Το Πανεπιστήμιο Ιωαννίνων

Τον Εθνικό Οργανισμό Φαρμάκων

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BIANEΞ A.E. ΒΙΟΜΗΧΑΝΙΑ ΦΑΡΜΑΚΩΝ ΕΤΑΙΡΕΙΑ ΤΟΥ ΟΜΙΛΟΥ ΓΙΑΝΝΑΚΟΠΟΥΛΟΥ

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Κάθε μέρα εργαζόμαστε ώστε να καλύψουμε ανικανοποίητες ιατρικές ανάγκες εστιάζοντας πρωτίστως στις θεραπευτικές κατηγορίες της ογκολογίας, της ουρολογίας, των λοιμώξεων και της μεταμόσχευσης εξελίσσοντας παράλληλα νέες θεραπευτικές κατηγορίες και αξιοποιώντας νέες τεχνολογίες έρευνας. Παραμένουμε αφιερωμένοι στο να ικανοποιούμε τις ανάγκες των ασθενών και η υποστήριξή μας προς αυτούς δεν θα πάψει ποτέ να υφίσταται.

Μέσω της αφοσίωσής μας να προσφέρουμε στους ασθενείς ελπίδα για ένα λαμπρότερο μέλλον, επιδιώκουμε να ηγηθούμε στις θεραπευτικές κατηγορίες που εξειδικευόμαστε, εστιάζοντας στις κατηγορίες όπου υπάρχουν ιατρικές ανάγκες που παραμένουν ανικανοποίητες. Μέσω της καινοτομίας, θα συνεχίσουμε να αναγνωρίζουμε και να αναπτύσσουμε νέους τρόπους για να καλυτερεύσουμε την υγεία των ασθενών.

Στην Astellas, εστιάζουμε στο να κάνουμε πραγματικότητα το *αλλάζοντας το αύριο.*

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