5th International Multithematic Scientific Bio-Medical Congress

Bio-medical Scientific Cyprus

Thursday, 2 November 2017, 13:30 - 20:00
Friday, 3 November 2017, 9:00 - 18:45
Saturday, 4 November 2017, 8:00 - 20:00

Cultural Center, European University Cyprus

15 Credits of Continued Medical Education (CME) will be awarded

International Recognition by Nature Publishers; cell Death & Disease Journal

The Congress is under the auspices of the Ministry of Health and the Cyprus Medical Association (CYMA)

Organized & Supervised by: Professor Dr Ioannis Patrikios

Sponsor:
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcome Address by Prof. Kostas Gouliamos</td>
<td>2</td>
</tr>
<tr>
<td>Welcome Address by Prof. George Petrikkos</td>
<td>4</td>
</tr>
<tr>
<td>Welcome Address by Prof. Dr Ioannis Patrikios</td>
<td>5</td>
</tr>
<tr>
<td>Chairmen and Speakers</td>
<td>7</td>
</tr>
<tr>
<td>Program</td>
<td>9</td>
</tr>
<tr>
<td>Speakers CVs</td>
<td>33</td>
</tr>
<tr>
<td>Abstracts</td>
<td>71</td>
</tr>
<tr>
<td>- Invited Abstracts</td>
<td>72</td>
</tr>
<tr>
<td>- Selected Abstracts</td>
<td>106</td>
</tr>
<tr>
<td>- Poster Abstracts</td>
<td>122</td>
</tr>
</tbody>
</table>
Welcome Address
By the Rector Professor Kostas Gouliamos

Distinguished Guests and Honorable Participants,

It is with great pleasure that I welcome you to the European University Cyprus, and with honor that I address the 5th Multidisciplinary Scientific Bio-Medical Congress 2017, “Biomedical Scientific Cyprus”.

European University Cyprus is an agile academic institution undergoing rapid growth while maintaining highest quality teaching and research; it has an exceptionally gifted student body, a world renowned faculty and innovative specialized disciplines; it is surrounded by first-rate research centers and laboratories and cutting-edge high tech infrastructures that open up a world of possibilities for multidisciplinary education and research.

European University Cyprus belongs to the largest international university organization, Laureate International Universities-- a worldwide network of Higher Education institutions founded in 1998 in the United States; it is currently made of more than 80 institutions in 28 countries, with more than 200 campuses and over 1,000,000 students worldwide.

Furthermore, Laureate International Universities is an international community of universities that encourages learning without boundaries, with a unique multicultural perspective.

European University Cyprus has secured a momentous distinction following the assessment by QS TOP UNIVERSITIES (QS StarsTM), the independent and most authoritative university-rating tool globally which places European University Cyprus among the top universities in the world with the highest distinction of 5-Stars in Teaching, Facilities, Inclusiveness, Social Responsibility and Internationalization. European University Cyprus is the only University in Cyprus to be rated by QS TOP UNIVERSITIES.

European University Cyprus promotes opportunities for long – term strategic partnerships with an impact on academics, the economy and society at large. Such a strategic Partnership was created when Microsoft s selected European University Cyprus to be its partner institution for the establishment of the only Microsoft Innovation Center in Cyprus and one of 100 that operate globally. The operation of The Microsoft Innovation Center (MIC) at European University Cyprus will have an enormous impact on students, faculty, IT professionals, researchers, the economy and society at large.

We are also more than pleased to say that European University Cyprus is now one of the 816 distinguished and historic universities that form the internationally recognized organization
Observatory Magna Charta Universitatum. Moreover, the European Commission has awarded European University Cyprus (EUC) one of the most prestigious international awards, recognizing its contribution to research excellence, the “HR Excellence in Research Logo”.

Dear Colleagues,

The European University Cyprus is becoming an Institution with high quality targets. Research, innovation, technology and excellence are our priorities and we are investing with emphasis on Biomedical-Sciences, with the latest, the launch of the Dentistry School since September 2017.

Exceptional events like this one have without any doubt our full support.

It is really an honor for us to have world known scientists, even Nobel laureates participating and lecturing in our Institution.

Saying this, I salute and welcome you all and warmly congratulate Professor Dr Ioannis Patrikios, Chairman and Faculty member of the School of Medicine for his initiative and hard work to organize and give flesh and bones to his idea; and for giving us the opportunity to successfully be here today.

I also acknowledge Bayer / Novagem Ltd, the diamond sponsor of the congress and all other sponsors and supporters for their contribution.

I wish you all a successful and productive congress.

Professor Kostas Gouliamos Rector,
European University Cyprus
Welcome Address
By Professor Dr George Petrikkos

Distinguished Guests and Honourable Participants,

It is with great pleasure that I welcome you to European University Cyprus and with honour that I address the 5th Multidisciplinary Scientific Bio-Medical Congress, entitled “Biomedical Scientific Cyprus”.
The European University Cyprus is becoming an Institution with high quality targets aiming to new frontiers of science, innovation, research and excellence. We are investing with particular emphasis on Bio-Sciences like the opening of the Medical School at our university in September 2013. We are very proud that from this academic year we opened the 1st Program in Dentistry.
High calibre events and symposia like this one, with distinguished scientists as speakers including Nobelists and participants from all over the world are the vehicles driving to the accomplishment of our goals and they have our full support.
Saying this, I salute and welcome every and each one of the congress participants and congratulate the Chairman Professor Dr. Ioannis Patrikios, Faculty member of the School of Medicine for his initiative and hard work to organize this event; and for giving us the opportunity to successfully be here today. I would like to thank our students in contributing for the smooth running of the congress. I would also like to acknowledge Bayer/Novagem Ltd, the sole sponsor of the congress for their genuine, valuable contribution.
I wish you all a successful and productive congress.

Professor Dr George Petrikkos
Acting Dean School of Medicine,
European University Cyprus”
Welcome Address
By Professor Dr Ioannis Patrikios

Dear Congress participants and guests
It is my great pleasure to welcome you to the 5th International Bio-Medical Scientific Cyprus Congress of the School of Medicine of the European University of Cyprus (EUC) that is taking place in Nicosia, Cyprus on the 2nd, 3rd and 4th of November 2017.

The School of Medicine of the EUC and Myself personally welcome all distinguished invited keynote and plenary speakers and the scientific community of Cyprus as well as the delegates from all over the world (Iran, Turkey, Greece, Nigeria, Poland, UK, Lebanon, Egypt, Italy, Germany and not only) that are attending this exceptionally high quality and high caliber Multidisciplinary Scientific Symposium. My warm regards and welcome extends to our very Special keynote speaker the Distinguished Professor Dr Lee Hartwell, winner of The Nobel Prize in Physiology or Medicine 2001 – for: “Cell Cycle Control”, that is going to give us a talk entitled “Educating physicians and scientists for the future”, live but unfortunately electronically due to distance problems.

As the founder and general organizer of the congress, I would like to thank the Ministry of Health and the Cyprus Medical Association (CYMA) for their support and recognition. Moreover, since this year our congress has been institutionalized by CYMA, something that happens for a first time ever; and this means a lot for the event itself but also for me and I would like very much to thank Dr Petros Agathaggelou the president of CYMA but also the rest of the committee members.

Once more, I would like to thank all of my fellow colleagues and friends that accepted the invitation to participate, travel, attend and share with us their unique and innovative scientific work of excellence as well as the executives of the European University of Cyprus (EUC) for their backing and trust in me and my abilities to organize this event at the highest possible level.

I thank all of my colleagues participating as chairmen/moderators of the session committees or the highly specialized round table workshop satellites; The Cyprus Society of Cardiology that is endorsing the workshop on cardiology as well as the Cyprus Neurological Society for doing the same, but also my colleagues here at the School of Medicine for their genuine support and willingness to help making this an unforgettable date of our calendar through the years.

It was my strong desire to establish this congress: “Biomedical Scientific Cyprus, (BSC)” to become an annual event with global recognition. Here we are for a fifth consecutive year. The target has been accomplished. Now the only thing we have to do is just to keep this congress at the level it deserves. The level of excellence as a medium of a Continued Medical Education for the professionals but also as an International arena of dissemination of novelties in Medical Science and that is the new promise of mine.
Not only that; for this year, our congress is upgraded to three-days event with participation and submission of more than 100 abstracts that are going to be published in the ISBN referenced congress abstract book and 55 scientific papers for the “Poster Sessions”; numbers that well exceeded all expectations and any previous participation.

Endorsing congresses by the level of original scientific work presented is not happening every day in the world. Our congress has been internationally recognized by one of the most trustable and reputable publishers in the world; through a Meeting Report in the Nature-Publisher-journal “Cell Death & Disease”.

This alone indicates the quality, seriousness and scientific prestige of the conference that was lounged exactly with the opening of the Medical School, five years ago and managed today to become an ordinance.

Finally, I would like to thank the sponsors of the congress, the diamond sponsor, Bayer and NOVAGEM LTD and especially Mr. Mario Christodoulou, the General Director of the aforementioned companies in Cyprus, for his genuine support; investing on continued learning, knowledge, innovation and excellence. Bayer/NOVAGEM is the sponsors of this event since our first meeting and we hope to have them for many more. Our thanks extend to our Gold sponsors Energo lab equipment and Scientronics, the silver sponsor Biotronics Analytical and Biomedical solutions and to the supporters, C & V Kriticos suppliers, Amatheus Travel, C Georgiou lab supplies, Taverna Zanettos and S&A Papoutsou Ltd.

This year, IMBMC will continue providing a higher interactive platform for Research and Innovation, Drug Discovery, Diagnostics and Clinical Management.

The conference is being held in early November one of the best times to visit the island and enjoy its natural beauty as well as history. I thank each and every one of you for being here with us.

I feel confident that you will enjoy both, the scientific program and the unique Mediterranean Island of Cyprus. I wish you all the best and a productive Congress.

Professor Dr Ioannis Patrikios
Acting Chair, Faculty of Medicine, School of Medicine, European University Cyprus
Founder, Chairman and General Congress Supervisor
## Chairmen / Speakers

<table>
<thead>
<tr>
<th>Chairmen</th>
<th>Plenary Speakers</th>
<th>Keynote Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Adamos Hadjipanagis</td>
<td>Prof. Dr Gerasimos Filippatos</td>
<td>Prof. Dr Leland Hartwell</td>
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<tr>
<td>Dr Akis Loizides</td>
<td>Prof. Dr Filippos Triposkiadi</td>
<td>Prof. Dr David Bates</td>
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<td>Dr Anastasis Stephanou</td>
<td>Prof. Dr Charis Antoniades</td>
<td>Prof. Dr Panayiotis Soucacos</td>
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<td>Dr Andreas kougialis</td>
<td>Prof. Dr Vasilis Vasilikos</td>
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<td>Dr Andreas Zachariades</td>
<td>Ass. Prof. Dr Konstantinos Toutouzas</td>
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<td>Dr Antonis Kirmizis</td>
<td>Prof. Dr Stavros Konstantinides</td>
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<td>Dr Christodoulos Kaisis</td>
<td>Dr Giorgos Andrikopoulos</td>
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<td>Dr Christos Eftichiou</td>
<td>Ass. Prof. Dr Ingeborg Friehs</td>
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<td>Dr Costas Michaelides</td>
<td>Dr Demetris Papamichael</td>
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<td>Dr Dimitrios Farmakis</td>
<td>Prof. Dr Gerry Melino</td>
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<td>Dr Dimitris Ntourakis</td>
<td>Ass. Prof. Dr Drimis Konstantininos</td>
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<td>Dr Elizabeth Johnson</td>
<td>Dr Stavros Charalampous</td>
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<td>Dr Elpida Nikolou</td>
<td>Dr Christos Christou</td>
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<td>Dr Evagoras Economides</td>
<td>Ass. Prof. Dr Marios Pantzaris</td>
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<td>Dr George Hadjigeorgiou</td>
<td>Prof. Dr Ioannis Patrikios</td>
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<td>Dr George Miltiadous</td>
<td>Prof. Dr Nikos Grigoriadis</td>
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<td>Dr Georgios Georgiou</td>
<td>Prof. Dr Nektarios Tavernarakis</td>
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<td>Dr Ilias Nikas</td>
<td>Prof. Dr George Hadjigeorgiou</td>
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<td>Prof. Dr Savvas Papacostas</td>
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<td>Dr Konstantinos Tsioits</td>
<td>Ass. Prof. Dr Demos Mitsikostas</td>
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<td>Dr Kyriakos Ioannou</td>
<td>Prof. Dr Achilleas Gravanis</td>
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<td>Dr Loizos Christodoulou</td>
<td>Dr Tassos Georgiou</td>
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<td>Dr Loizos Loizou</td>
<td>Dr George Vrakas</td>
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<tr>
<td>Dr Maria Alexandrou</td>
<td>Ass. Prof. Dr Hans Chatzis</td>
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<td>Dr Marios Loizou</td>
<td>- Arkouli Nefeli</td>
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<td>Dr Marios Pantzaris</td>
<td>- Boutsikos Ioannis</td>
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<td>Dr Michales Hadjigavriel</td>
<td>- Brockman Tamara-Jade</td>
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<td>- Capsis Thisseas</td>
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<td>- Charitaki Jenny</td>
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<td>- Eniaiyewu Barbara</td>
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<td>- Georgiou Andrew</td>
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<td>- Gerakini Anna-Maria</td>
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</tr>
</tbody>
</table>

**Special Thanks** to the Medical students that have contributed to the organization of the conference; and Professor Dr Elizabeth Johnson for her leading role organizing the students.

- Gravdahl Nora
- Grekou Themis
- Kiosoglous L. Anthony
- Louca Stephanie
- Mahmoodi Maryam
- Papadimitriou Filippos
- Salamouri Myrsini
- Shartouni Ranim
- Strouthou Eleana
- Tsaroucha Aristea

**Independent Poster Award Committee**

- Prof. Dr Alberto Mantovani
- Prof. Dr Archileas Gravanis
- Ass. Prof. Dr Dimas Konstantinos
# SAMSUNG Portable & Benchtop Clinical Analyzers

## Product List

<table>
<thead>
<tr>
<th>Product Names</th>
<th>Parameters</th>
<th>Article Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samsung LABGEO® IB10</td>
<td>Troponin I Test</td>
<td>BCA-B10</td>
</tr>
<tr>
<td></td>
<td>Immunoassay Analyzer</td>
<td></td>
</tr>
<tr>
<td>Samsung LABGEO® IB</td>
<td>CHF Test</td>
<td>IVR-B07</td>
</tr>
<tr>
<td></td>
<td>Cardiac 3-in-1 Panel Test</td>
<td>IVR-B08</td>
</tr>
<tr>
<td></td>
<td>D-Dimer Test</td>
<td>IVR-B09</td>
</tr>
<tr>
<td></td>
<td>SOB Cardiac 3 Panel Test</td>
<td>IVR-B11</td>
</tr>
<tr>
<td></td>
<td>beta-hCG Test</td>
<td>IVR-B12</td>
</tr>
<tr>
<td></td>
<td>TSH Test</td>
<td>IVR-B15</td>
</tr>
<tr>
<td></td>
<td>B-R-A-H-M-S PCT</td>
<td>IVR-B18</td>
</tr>
<tr>
<td>Samsung LABGEO® PT10</td>
<td>Hepatic Test 9</td>
<td>IVR-PT01</td>
</tr>
<tr>
<td></td>
<td>Lipid Test 5</td>
<td>IVR-PT03</td>
</tr>
<tr>
<td></td>
<td>Biochemistry Test 9</td>
<td>IVR-PT05</td>
</tr>
<tr>
<td></td>
<td>HbA1c Test</td>
<td>IVR-PT07</td>
</tr>
<tr>
<td>Samsung LABGEO® HC10</td>
<td>WBC 3-part differential, 18 parameters: WBC, LYM, MON, GRA, LYMK, MONK, GRAW, Hb, HCT, RBC, MCV, MCH, RDW, MCHC, PLT, PCT, MPV, PDW</td>
<td>ND-C10A</td>
</tr>
<tr>
<td></td>
<td>Diluent</td>
<td>IVR-C01A</td>
</tr>
<tr>
<td></td>
<td>Lyse</td>
<td>IVR-C03A</td>
</tr>
<tr>
<td></td>
<td>Cleaner</td>
<td>IVR-C04A</td>
</tr>
<tr>
<td></td>
<td>Hypocleaner</td>
<td>IVR-C05A</td>
</tr>
</tbody>
</table>

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Bio-medical
Scientific
Cyprus

Program
Program

THURSDAY 2-11-2017

5th International Bio-Medical Scientific Cyprus Congress
School of Medicine, European University Cyprus
November 2 - 4, 2017
(Institutionalized by the Cyprus Medical Association, 15 C.M.E)

12.30 –1:45  Registration / Coffee

Opening Ceremony

1:45 – 2:10  Introduction to the EUC School of Medicine

Saxophone Ensemble of EUC
The Saxophone Quartet of European University Cyprus will present a varied program with works from Italy, USA, Spain/Greece and Ireland. The quartet is comprised of Karl Tipp (Estonia) – soprano saxophone, Vicky Siafaka (Greece) – alto saxophone, Christos Papadopoulos (Cyprus) – tenor saxophone and Nicos Kaiafas (Greece) – baritone saxophone.

Associate Professor Yiannis Miralis Conductor
2:15 – 2:45  Welcome Addresses

Prof. Dr Ioannis Patrikios
Congress Chair and Acting Chair of the School of Medicine, European University Cyprus

Prof. Dr Georgios Petrikkos
Dean of the School of Medicine, European University Cyprus

Prof. Kostas Gouliamos
Rector, European University Cyprus

Representatives of Cypriot Government and Cyprus Medical Association
- General Director of Health, Ministry of health on Behalf of the President N. Anastasiades Dr. Christina Yianaki
- President of Parliament, Mr Demetris Silouris
- President of Cyprus Medical Association, Dr Petros Agathaggelou

Advances in Cardiology
Cardiology Research and New Potential Treatment Approaches

2:45 – 3:10  Prof. Dr Gerasimos Filippatos
University of Athens
Cardiorenal syndrome: From bench to bedside and back
Chairs: Petros Agathaggelou, Dimitrios Farmakis
3:10 – 3:35  Prof. Dr Filippos Triposkiadis  
*Director, Department of Cardiology Larissa University Hospital, Larissa, Greece*

**Left Ventricular Ejection Fraction: An Index of Left Ventricular Systolic Function?**

**Chairs:** Petros Agathaggelou, Christos Eftichiou

3:35 – 3:55  COFFEE and Snack

3:55 – 4:20  Prof. Dr Charis Antoniades  
*Oxford University Hospitals NHS Foundation Trust*

**Perivascular adipose tissue as a window to the coronaries**

**Chairs:** Petros Agathaggelou, Christos Eftichiou

4:20 – 4:45  Prof. Dr Vassilios Vassilikos  
*Medical School, Aristotle University of Thessaloniki*

**Atrial fibrillation: what do we know and what we can do in 2017**

**Chairs:** Stylianos Hadjistillis, Michalis Neofytou

4:45 – 5:10  Ass. Prof. Dr Konstantinos Toutouzas  
*University of Athens*

**New advances in percutaneous treatment of aortic and mitral valve**

**Chairs:** Stylianos Hadjistillis, Michalis Neofytou

5:10 – 5:30  COFFEE
5:30 – 5:55  Prof. Dr Stavros Konstantinides
University of Mainz, Germany; Democritus University of Thrace, Greece

The Transition from Acute Pulmonary Embolism to Chronic Thromboembolic Pulmonary Hypertension: Pathophysiology, Clinical Corse, and Implications for Patient Management and Follow-up

Chairs: Georgios Georgiou, Economides Evagoras

5:55 – 6:20  Dr Giorgos Andrikopoulos
Director of Electrophysiology and Pacing department, Henry Dunant Hospital Center, Athens, Greece

Prevention and Treatment of Ischemic Heart Disease and Atrial Fibrillation

Chairs: Economides Evagoras, Georgios Georgiou

6:20 – 6:45  Ass. Prof. Dr Ingeborg Friehs
Department of Cardiac Surgery, Boston Children’s Hospital and Harvard Medical School, Boston MA

Mitochondrial transplantation - a novel therapy for cardiac disease

Chairs: Dimitrios Farmakis, Elpida Nikolousi
6:50 – 8:30
Room: Amphi-
theater Beta

Under The Auspices of the Cyprus Society of Cardiology

In Parallel to the Program: Satellite workshop: Update on Thrombosis Therapeutic approach – Presentation and discussion of cases

Prof. Dr Gerasimos Filippatos: Heart Failure and Anti-coagulation

Prof. Dr Stavros Konstantinides: Deep Vein Thrombosis and Pulmonary Embolism (DVT /PE)

Dr Andrikopoullos Giorgos: Diagnosis, Cardioversion and Ablation of Atrial Fibrillation (AF). Clinical Dilemmas on Thromboembolic Risk Management of AF.

Ass. Prof. Dr Konstantinos Toutouzas: AF– Coronary Artery Disease (CAD)-Percutaneous Coronary Intervention

Prof. Dr Filippos Triposkiadis: Current Management of Heart Failure with Reduced Ejection Fraction

Prof. Dr Vassilios Vassilikos: Hemoptysis and dyspnea in a patient after atrial fibrillation ablation

Chair/Moderation: Petros Agathaggelou (president of Cyprus Medical Association) and Georgios Georgiou (president of Cyprus Cardiology Association)
Under The Auspices of Cyprus Neurological Society

6:50 – 8:15
Room: Omega

In Parallel to the Program: Satellite workshop: Update on Multiple Sclerosis Therapeutic approach – Presentation and discussion of cases

Prof. Dr George Hadjigeorgiou
Prof. Dr Nikos Grigoriadis
Dr Angelos Gregoriou
Ass. Prof. Dr Marios Pantzaris

Chair/Moderation: Michaelides Costas (president of Cyprus Neurological Society)

8:30 – 9:15 Wine & Cheese

FRIDAY 3-11-2017

8:00 – 9:15 Registration / Coffee

Advances in CANCER Therapy
Cancer Research and New Potential Treatment Approaches
9:15 – 9:40  Dr Demetris Papamichael  
*Director of Medical Oncology at the Cyprus Oncology Centre in Nicosia*

**The Changing Landscape of Colorectal Cancer Management**  
*Chairs: Antonis Kirmizis, Demetris Ntourakis*

9:40 – 10:05  Prof. Dr Gerry Melino  
*University of Rome Tor Vergata, Italy; Oxford University, London, UK*

**Mutp53 & TAp73 regulates tumour microenvironment via hypoxia-inducible factor-1α**  
*Chairs: Anastasis Stephanou, Antonis Kirmizis*

10:05 – 10:30  Ass. Prof. Dr Dimas Konstantinos  
*University of Thessaly, School of Medicine*

**Sigma Ligands as Potential Novel Targeted Anticancer Therapies**  
*Chairs: Michales Hadjigavriel, Andreas Zachariades*

10:30 – 10:55  Prof. Dr Anastasis Stephanou  
*School of Medicine, European University Cyprus*

**Annonasin From Graviola Extract Promotes Selective Cancer cell death In vitro and In vivo via NKA and SERCA Downregulation Pathways**  
*Chairs: Andreas Zachariades, Michales Hadjigavriel*
10:55 – 11:20  COFFEE BREAK

11:20 – 11:45  Ass. Prof. Dr Andreas Hadjisavvas

*The Cyprus Institute of Neurology and Genetics-Cyprus*

*School of Molecular Medicine, Cyprus*

Applications of pharmacogenetics; our experience the last six years

*Chairs*: Antonis Kirmizis, Adamos Hadjipanagis

11:45 – 12:10  Dr Christiana Neophytou

*Post Doc of Andreas Constantinou at the University of Cyprus*

Nanoparticle applications in cancer chemoprevention and therapy

*Chairs*: Andreas Zachariades, Adamos Hadjipanagis

12:10 – 12:35  Assist. Prof. Dr Giorgos Apidianakis

*University of Cyprus*

Flies to Humans - Humans to Flies: A Virtuous Circle of Colorectal Cancer Prevention

*Chairs*: Demetris Ntourakis, Constantine Hadjileontis

*Immunotherapy as a Novel Cancer Treatment Approach*
12:35 – 13:00  Prof. Dr. Barbara Seliger

*Martin Luther University, Institute for Medical Immunology, Germany*

**Immune escape of tumors: Emerging concepts and therapeutic opportunities**

**Chairs:** Loizos Loizou, Nikos Grigoriadis

13:00 – 15:00  **LUNCH BUFFET**

**Poster Session**

**Immunotherapy as a Novel Cancer Treatment Approach**

15:00 – 15:25  Dr Licia Rivoltini

*Director, Fondazione IRCCS Instituto Nazionale dei Tumori, Milano, Italy*

**Exploiting myeloid cells as prognostic biomarker and therapeutic target in cancer patients**

**Chairs:** Loizos Loizou, Nikos Grigoriadis

15:25 – 15:50  Prof. Dr George Chrousos

*National and Kapodistrian University of Athens School of Medicine, Athens, Greece*

**Stress, Genetics, Epigenetics and Human Evolution and Development**

**Chairs:** George Hadjigeorgiou, Andreas Zachariades
15:50 – 16:15  Prof. Dr Elizabeth Johnson
National and Kapodistrian University of Athens School of Medicine, Athens, Greece; School of Medicine, European university Cyprus, Nicosia, Cyprus

Neuroanatomy of Stress: Unraveling the Neural Circuits in Stress & Anxiety Disorders

Chairs: Christodoulo Kaisis, George Hadjigeorgiou

Keynote Speech

16:15 - 16:45  Prof. Dr Leland Hartwell
Arizona State University, USA
The Nobel Prize in Physiology or Medicine 2001 – for: “Cell Cycle Control”

Speech Title:
“Educating physicians and scientists for the future”

Chairs: Elizabeth Johnson, Christodoulos Kaisis

16:45 – 17:05  COFFEE BREAK
Satellite by Scientronics

17:05 – 17:30  Dr Florian Graedler
Senior Product Specialist Distributors EMEA, in Illumina Inc.

From Microarrays to Next Generation Sequencing: The impact of genomics on modern medicine

Chairs: Anastasis Stephanou, Ilias Nikas

State of the Art Non Invasive Technologies as a Tool for New Therapies and prognosis
17:30 – 17:55  Prof. Dr Philippos C. Patsalis
Distinguished Professor at the Cyprus Institute of Neurology and Genetics and the Cyprus School of Molecular medicine; Founder and CEO  NIPD Genetics

The New Generation Non Invasive Prenatal Test

Chairs: Anastasis Stephanou, Elpida Nikolousi

Neurogenetics

17:55 – 18:20  Prof. Dr Kyproula Christodoulou
The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus

Translational Neurogenetics Towards the Identification of Targets for the Development of Therapeutic Strategies

Chairs: Vakis Papanastasiou, Kyriakos Ioannou

18:20 – 18:45  Prof. Dr Marios Cariolou
The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus

Human identity testing: How “anonymous” can we be?

Chairs: Kyriakos Ioannou, Vakis Papanastasiou

18:45 – 20:00  Wine & Cheese
SATURDAY 4-11-2017

8:00 – 8:45 Coffee

Polythematic Sessions

8:45 – 9:10 Prof. Dr Leondios G. Kostrikis

University of Cyprus

HIV Disease: From Biology to Chemotherapeutics and Beyond

Chairs: Niki Paphitou, Michalis Petrou

9:10 – 9:35 Prof. Dr Alberto Mantovani

Senior toxicologist of the Italian National Health Institute (Istituto Superiore di Sanità –ISS) and also an expert of the European Food Safety Authority

Emerging issues in the assessment of endocrine disrupting chemicals

Chairs: Michalis Petrou, Maria Alexandrou

9:35 – 10:00 Dr Stavros Charalambous

President of Cyprus Urological Association. In private practice: founder of the Institute of Fictional & Reconstructive Urology in Limassol, Cyprus

My Current approach to female urinary incontinence

Chairs: Ziat Milat, Kyriakos Ioannou
10:00 – 10:25  Dr Christos Christou  
*American Heart Institute*

**Carotenoids and Cardiovascular Diseases**

**Chairs:** Petros Agathaggelou, George Miltiadous

10:25 – 10:40  **COFFEE BREAK**

10:40 – 11:10  Prof. Dr Panayiotis Soucacos  
*Orthopaedic Research & Education Center  
University of Athens, School of Medicine*

**Microsurgery in the New Era of Managing Tissue Loss: Past, Present and Future of Replantation and Allotransplantation**

**Chairs:** Akis Loizides, Christodoulou Loizos, Andreas Kougialis

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**Natural Products, Pharma and Complementary Medicines: Novelties and Emerging Targets**

**Advances in Neurology and Neurodegenerative Diseases**

**Research and New Potential Treatment Approaches**

*Neurodegenerative Diseases-Multiple Sclerosis- Neuroprotection, Neuroregeneration  
&  
Natural anti-inflammatory Structured molecules (PUFA) and Antioxidant Vitamins/ Nutrients*
11:10 – 11:30 Ass. Prof. Dr Marios Pantzaris
The Cyprus Institute of Neurology and Genetics-Cyprus
School of Molecular Medicine, Cyprus

PUFA and their Biological Effect

Chairs: Andreas Kougialis, Vakis Papanastasiou

11:30– 11:50 Prof. Dr Ioannis Patrikios
Chairman, School of Medicine, European University Cyprus

Specific Omega-3, Omega-6 Polyunsaturated Fatty Acids and γ-Tocopherol in the Therapy of Relapsing Multiple Sclerosis, How and Why: the Paradigm of NEUROASPIS® PLP10 Intervention Efficacy

Chairs: Andreas Kougialis, Vakis Papanastasiou

Keynote Speech

11:50 – 12:20 Prof. Dr David Bates
Emeritus Professor of Clinical Neurology at Newcastle University, UK; past Chairman of the International MS Forum, past Chairman of the Medical Research Advisory Committee of the MS Society of Great Britain and Northern Ireland

Dietary Supplementation in Multiple Sclerosis

Chairs: George Hadjigeorgiou, Marios Pantzaris, Nikos Grigoriadis

12:20 – 13:30 LUNCH BUFFET

Poster Session
13:30 – 13:55  Prof. Dr Nikos Grigoriadis  
*AHEPA University Hospital, Thessaloniki, Greece*

*Is neurodegeneration an absolutely inflammation-related process in MS?*

**Chairs:** Andreas kougialis, Vakis Papanastasiou

**Research on NEUROLOGICAL Diseases / Dementias**

13:55 – 14:20  Prof. Dr Nektarios Tavernarakis  
*Medical School of the University of Crete, in Heraklion, Greece and Directors at the Foundation for Research and Technology-Hellas (FORTH)*

*Autophagic pathways in health and disease: Mitophagy and neurodegeneration*

**Chairs:** Anastasis Stephanou, Adamos Hadjipanayis

14:20 – 14:45  Prof. Dr George Hadjigeorgiou  
*Larisa School of Medicine*

*Diagnosis of muscle diseases in the era of next generation sequencing.*

**Chairs:** Nikos Grigoriadis, Elpida Nikolousi
14:45 – 15:10  Prof. Dr Savvas Papacostas
The Cyprus Institute of Neurology and Genetics-Cyprus
School of Molecular Medicine, Cyprus

Sudden unexpected death in epilepsy: The Cyprus experience in comparison with international data.

Chairs: Nicos Gregoriades, Marios Pantzaris

15:10 – 15:25  COFFEE BREAK

15:25 – 15:50  Ass. Prof. Dr Demos Mitsikostas
Aeginition Hospital; National & Kapodistrian University of Athens

NOCEBO in Neurological Disorders and Headache

Chairs: Christodoulos Kaisis, Marios Pantzaris

15:50 – 16:15  Prof. Dr Achilleas Gravanis
School of Medicine, University of Crete

Regenerating neuroimplants in spinal cord injury

Chairs: George Hadjigeorgiou, Christodoulos Kaisis
16:15 – 16:40  Dr Tassos Georgiou  
*Ophtalmos clinic, Nicosia, Cyprus*

**Therapeutic potential of omega 3 fatty acid supplementation in Macular Degenerations**

**Chairs:** Marios Loizou, Konstantinos Tsioutis

16:40 – 17:05  Dr George Vrakas  
*Transplant Surgeon, Oxford University, UK*

**Current Concepts in Transplantation: Combining Vascularized Composite Allografts with Intestinal Transplants**

**Chairs:** Marios Loizou, Christodoulos Kaisis

17:05 – 17:20  **COFFEE BREAK**
**Oral Presentation (Selected Abstracts)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Authors</th>
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<tbody>
<tr>
<td>17:20 – 17:30</td>
<td>The Association Between Brain Iron Accumulations with Blood Iron Metabolism Markers in Multiple Sclerosis Patients”</td>
<td>Dr. Seyed Aidin Sajedi ¹, Dr. Fahimeh Abdollahi ², Dr. Nastaran Majdinasab ³, Dr. Mohammad Saghatoleslami ⁴, Dr. Hamidreza Saligheh Rad ⁵,⁶, Dr. Ali Reza Ghorbani ⁴, Dr. Nooshin Kiarashi ⁷,⁸, Kavoos Bahraami ⁹, Dr. Ahmad Soltani Shirazi ⁹</td>
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<tr>
<td>17:30 – 17:40</td>
<td>Stroke Outcomes in Polish Pediatric Patients With Arterial Ischemic Stroke Depending on Gender</td>
<td>Beata Sarecka-Hujar¹, Ilona Kopyta²</td>
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<tr>
<td>17:40 – 17:50</td>
<td>Molecular Modelling Studies on the Recently-Solved Crystal Structure of Human Histone Deacetylase 6 (HDAC6) Catalytic Domain 2 Complexed with Known HDAC Inhibitors and the Design of Potential Inhibitors for Cancer Therapy.</td>
<td>Abdullahi Ibrahim Uba⁵,⁶, Kemal Yelekci⁶</td>
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<tr>
<td>17:50 – 18:00</td>
<td>Detection of Aberrant Methylation in Relapsing-Remitting Multiple Sclerosis with MS-MLPA</td>
<td>Maria Sokratous¹, Efthimios Dardiotis¹, Eleni Bellou¹, Zisis Tsouris¹, Amalia Michalopoulou¹, Maria Dardioti¹, Vasileios Siokas¹, Dimitrios Rikos¹, Georgios Tsivgoulis², Dimitrios Bogdanos³,⁴, Georgios M. Hadjigeorgiou¹</td>
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<tr>
<td>18:00 – 18:10</td>
<td>Specific Delivery of Therapeutic Sequences in Muscle by RNA Aptamers</td>
<td>Philippou S¹,⁴, Mastroyiannopoulos NP¹,⁴, Makrides N²,⁴, Kleanthous M³,⁴, Lederer CW³,⁴ and Phylactou LA¹,⁴*</td>
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<td>18:10 – 18:20</td>
<td>Variations of Transverse Foramina in Cervical Vertebrae: what Happens to the Vertebral Artery?</td>
<td>Aristeidis Zabis¹, Vasileios Mitrousis¹, Nikolaos Galanakis², Nikoletta Chalampalaki², Dimitrios Arvanitis¹, Apostolos Fyllos¹, Apostolos Karantanas²</td>
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Chairs: Marios Pantzaris, Vakis Papanastasiou

18:20 – 18:30 (Nicosia – Cyprus) Molecular genetic diagnosis of cardiomyopathies by Next Generation Sequencing pane
Paschalis Nicolaou¹², Christina Votsi¹², Loizos Antoniades³, Kyproula Christodoulou¹²

18:30 – 18:40 (Nicosia – Cyprus) Full Genome Sequencing and Phylogenetic Analysis of the First West-Nile Virus Identified in Cyprus
Richter J.¹, Tryfonos C.¹, Tourvas A.², Floridou D.², Papit- tou N.I.³, Christodoulou C.¹

18:40 – 18:50 (Nicosia – Cyprus) IgG from Multiple Sclerosis Patients Positive for Antiphospholipid Antibodies Increases the Activation of p38 MAPK and p65 NF-κB
Natalia Filippidou¹, Marios Pantzaris¹, Christina Christodoulou², Anastasia Lambrianides¹

18:50 – 19:00 (Nicosia – Cyprus) Gene Therapy of β-Globinopathies: Conceivable, Achievable, Affordable?
Carsten Werner Lederer

19:00 – 19:10 (Nicosia – Cyprus) Immune Cytolytic Activity Correlates with Mutational Burden and Deregulated Expression of Inhibitory Checkpoint Molecules in Colorectal Cancer.
Apostolos Zaravinos¹, Konstantinos Roufas², Christodoul- los Efstathiades², Christos Dimopoulos²

19:10 – 19:20 (Nicosia – Cyprus) Non-invasive prenatal testing of microdeletion syndromes
George Koumbaris¹, Kyriakos Tsangaras¹, Petros Mina¹, Charalambos Loizides¹, Achilles¹, Achilleos¹, Elena Kypri¹, Marios Ioannides¹, Philippos C Patsalis¹
19:20 – 19:30 (Nicosia – Cyprus)  
Reversal of Fetal Globin Silencing Through Isoform-Specific Disruption of the BCL 11A Transcription Factor

Constantinos C. Loucari\textsuperscript{a,c}, Thamar B. van Dijk\textsuperscript{b}, Petros Patsali\textsuperscript{a}, Panayiota Papasavva,\textsuperscript{a,c} Maria Sitarou\textsuperscript{d}, Soteroulla Christou\textsuperscript{d}, Sjaak Philipsen\textsuperscript{b}, Carsten W. Lederer\textsuperscript{a,c,*}, Marina Kleanthous\textsuperscript{a,c,*}

19:30 – 19:40 (Nicosia – Cyprus)  
A novel localization and function of acid ceramidase, a key regulatory enzyme of ceramide metabolism

Kalia Kyriakou, Judith Elizabeth Sleeman, Anthi Drousiotou, Anna Malekkou  

\textbf{Chairs:} Elisabeth Johnson, Konstantinos Hadjileontis

19:40 – 19:50 (Nicosia – Cyprus)  
\textit{Poster Awards}  
\textit{Closing Ceremony}

\textit{Congress Chair, Prof. Dr Ioannis Patrikios}

I.Patrikios  
Founder and Congress Chair

All coffee breaks and lunch are sponsored by Bayer Novagem.
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Feature Highlights
• Affordable-to-acquire and cost-efficient to run, even with low numbers of samples
• Push-Bottom Operation and Easy Data Analysis Walk away library-to-results solution with onboard data analysis
• Highly Flexible to Fit Research Demands Supports a broad range of DNA and RNA sequencing applications for examining single genes to entire pathways
• End-to-End Support from assay design through data analysis
• Streamlined Sequencing Workflow
• Able to provide up to ~7.5 Gb good Quality Data (>80%>Q30) per day
Bio-medical Scientific Cyprus

Speakers CVs
Lee Hartwell, PhD, led a research team at the Genetics Department, University of Washington, from 1968 to 1997 studying the genetic control of cell division in yeast. He was President and Director of the Fred Hutchinson Cancer Research Center from 1997-2010. He received the 2001 Nobel Prize in Physiology or Medicine.

At Arizona State University (ASU), Dr. Hartwell works in health and education. At ASU he leads the Honey Bee Project, a series of clinical trials investigating the application of wearable sensors to clinical medicine. He advises a Biosignatures Center at Chang Gung University and Hospital system in Taiwan that is developing biomarker tests for oral cancer and other diseases. In education, Dr. Hartwell leads a team devoted to K-8 teacher education in Sustainability Science.

Other honors include the Albert Lasker Basic Medical Research Award, the Gairdner Foundation International Award, the Alfred P. Sloan Award in cancer research, and the Genetics Society Medal of Honor. He is a member of the National Academy of Sciences and a foreign member of Academia Sinica in Taiwan.
Professor Dr David Bates
Emeritus Professor of Clinical Neurology at Newcastle University, UK; past Chairman of the International MS Forum, past Chairman of the Medical Research Advisory Committee of the MS Society of Great Britain and Northern Ireland

David Bates is Emeritus Professor of Clinical Neurology at Newcastle University, UK. He served as Chairman of the Joint Colleges Working Party on the Vegetative State and Criteria for Brain Stem Death, London, UK, and Chairman of the Consensus Conference on the Epilepsies for the Royal College of Physicians, Edinburgh, UK. He is past Chairman of the International MS Forum, past Chairman of the Medical Research Advisory Committee of the MS Society of Great Britain and Northern Ireland, and Former Editor of the International MS Journal.

His research interests are in vascular disease, coma and the unconscious patient, and in MS. His current research is predominantly in clinical trials of novel therapy in MS and in the role of mitochondria in protecting and repairing axons in the more chronic phases of the disease.

Professor Bates studied medicine at Downing College, Cambridge University, UK, and at Middlesex Hospital, London, UK, before training in neurology at the University of Newcastle upon Tyne and, as Harkness Fellow, at the Mayo Clinic, Rochester, Minnesota, USA. He has published more than 200 peer-reviewed papers, edited three textbooks and contributed chapters to more than 35 books.
Dr. Panayotis N. Soucacos served as Professor and Chairman of the Department of Orthopaedic Surgery at the University of Ioannina (1980-2002) and at the University of Athens (2002-2008). In 2012, he was appointed the first President of the Board of Trustees of the University of Ioannina. Over the last 40 years he has been active in academic medicine, maintaining long-standing international inter-university collaborations, establishing internationally renowned clinical units such as, Duke University Medical Center, USC and University of Pennsylvania. He has spearheaded the development of orthopaedic research laboratories and in 2012 received a grant to establish the “Orthopaedic Research and Education Center” (OREC) to foster post-graduate research at Attikon University Hospital. The National & Kapodistrian University of Athens, unanimously voted to name the center “Panayotis N. Soucacos”. Of the seven Medical Schools in Greece, former trainees of Professor Soucacos are now full tenured Professors and/or Chairmen in 5 Departments. More importantly, all academic Departments of Orthopaedics and Hand Surgery throughout Greece have faculty members trained and mentored by Professor Soucacos, of whom he has fostered over 93 fellows to train further in internationally renowned centers. Five of his former fellows are currently professors in the United States and Europe. In all, Professor Soucacos has fostered the growth of Orthopaedic Surgery in Greece, spearheading and promoting throughout the country outstanding, independent clinical work and scientific investigations with international recognition.

The bulk of Professor Soucacos’ scholarly work has been aimed at the application of microsurgery for hand and upper extremity reconstruction. He is member of the Editorial Board of several distinguished International and Greek Orthopaedic Journals and has spoken extensively in all areas in orthopaedics throughout the world. He has served as a Visiting Professor at over 30 Universities around the world, is an active member of numerous orthopaedic scientific organizations, and as served as President in several societies including the World Society for Reconstructive Microsurgery. Professor Soucacos has made over 500 scientific contributions to the international scientific literature, and as served as a Guest Editor of over 18 special issues. In recognition of Professor Soucacos’ scholarly impact in academic medicine, he has received several distinguished awards, including the Award for Academic Excellence by the President of the Greek Democracy in 1996, the Doctoris Honoris Causa from the University of Cluj in 2008, and the title of Honorary Professor from the University of Ioannina in 2012. For fostering growth in the field of Hand Surgery in the international arena, he was recognized as a “Pioneer of Hand Surgery” in 2013 by the International Federation of Societies for Surgery of the Hand.
Associate Professor Dr Marios Pantzaris
*The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus*

He got his training in Neurology in 1995 in Thessaloniki, Greece. He has been trained in Carotid Duplex – Doppler ultrasonography in London, St Mary’s Hospital in 1995 and in 1999 he was a visiting doctor in an acute stroke unit in Massachusetts General Hospital, Harvard University Boston, USA.

He is working at the Cyprus Institute of Neurology and Genetics as a Senior Neurologist in the Neurological Dept and he is the Head of the Neurology Clinic C and the Neurovascular Department.

He has a huge experience in carotids – transcranial ultrasound and he has participated in many research projects and publications in this area.

He is also head of the Multiple Sclerosis (MS) clinic with more than 1000 patients where he is running research projects towards the etiology and therapy of MS. He is also interested in movement disorders and pain. With the collaboration of the Cyprus Functional Neurosurgery team they have started operating patients with Parkinson disease (Deep Brain Stimulation) as well as neuropathic pain (Spinal Cord Stimulation).

He has given many lectures about MS, carotids ultrasound stroke and Parkinson’s disease in Cyprus and abroad.
Speakers CVs

Professor Dr Gerasimos Filippatos

*Heart Failure Unit at Athens University Hospital Attikon, Greece and Past President of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)*

Professor Gerasimos Filippatos heads the Heart Failure Unit at Athens University Hospital Attikon, Greece. He studied at the University of Patras, Greece, and earned his doctorate in physiology and critical care cum laude from the University of Athens. He subsequently completed his clinical training in internal medicine, cardiology, critical care, heart failure, and transplantation in Athens Greece, Chicago USA; and Cambridge UK.

Dr Filippatos is Immediate Past President of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). He has served as Chair of the Clinical Section and the Committee on Acute Heart Failure of the HFA, and as Chair of the ESC’s Working Group on Acute Cardiac Care. He was also Coordinator of the ESC Congress Programme Committee for Heart Failure and Acute Cardiac Care, member of the ESC Practice Guidelines Committee and ACC/AHA HF Guidelines Writing Committee, and International Governor of the American College of Chest Physicians. His main research interest is acute and chronic heart failure, comorbidities and atrial fibrillation and he has been the principal investigator for numerous clinical trials and registries.

Dr. Filippatos is Associate Editor of the International Journal of Cardiology and European Heart Journal, and member of the Editorial Board and Guest Editor of many Cardiology and Critical Care Journals. He has published over 400 articles in peer-reviewed journals and authored more than 30 book chapters including the “Acute Heart Failure” chapter in Braunwald’s 2011 edition and Oxford Desc Reference: Cardiology. Moreover, he has (co) edited 5 books including the European Society of Cardiology Textbook of Acute and Intensive Cardiac Care, Highly Commended in the 2011 British Medical Association Medical Book Awards; in 2014 presented the book Heart Failure: The Expert’s Approach and in 2016 the pocket Treatment Algorithms in Heart Failure.

Prof. Filippatos is in the Thomson Reuters list of Highly Cited Researchers. Honorary Member of many Cardiac Societies: ie French Cardiac Society, Romanian Cardiac Society, Hungarian Cardiac Society.
Dr. Triposkiadis, Professor of Cardiology of the University of Thessaly and Director of the Department of Cardiology at Larissa University Hospital. He has also served as Chairman of the Internal Medicine Sector of the University of Thessaly and Chief Medical Officer of the Larissa University Hospital. Dr. Triposkiadis is a member of several national and international scientific societies including the European Society of Cardiology, the American College of Cardiology, the Heart Failure Association (HFA) of the European Society of Cardiology (Fellow) and Vice president of the Hellenic Society for the Study and Research of Heart Failure. Dr. Triposkiadis is nationally and internationally known for his research work on the physiology and pathophysiology of the left atrium, the significance of comorbidities in heart failure, the pathophysiology and management of heart failure, the sympathetic nervous system, and the physiological significance as well as the clinical implications of the derangements of the left ventricular ejection fraction. He has served as a member in HFA guideline committees and is the editor of one Textbook of Cardiology (two editions, Athens 2003 and Athens 2016) which has been adopted by several Hellenic Medical Schools and co-editor of one Textbook on Diabetes-Heart-Vessels (Athens 2010).
Charis studied Medicine in Athens University Medical School and graduated with hons (top 3%) in 2000. He was awarded his PhD title with hons on the genetics of premature myocardial infarction, and his PhD studies he won multiple Young Investigator’s award (YIA) competitions, including those of the American College of Cardiology, the European Society of Cardiology (ESC) twice, the International Society of Heart Research and others. In 2011 he became a Principal Investigator in the University of Oxford and he is currently an Associate Professor of Cardiovascular Medicine. He is funded by the British Heart Foundation, the National Institute of Health Research (NIHR), the European Commission, the NovoNordisk foundation and other funding bodies. His research is focused on the study of the cross-talk between adipose tissue and the cardiovascular system in humans, with specific interest in molecular imaging of vascular inflammation. He directs the Oxford Heart Vessels and Fat programme, with total funding over £5m, and recently he has developed a novel CT-based technology that detects coronary inflammation non-invasively. He has published more than 220 full length papers on this topic, and he has an h index of 55 with >8.5k citations (April 2017). He practices as a Consultant Cardiologist at Oxford University Hospitals NHS Trust, and he also runs the Trust’s hypertension service. In 2011 he was honoured with the prestigious “K Samaras” award of the Hellenic Heart Foundation and the University of Athens, and in 2015 he gave the “John French” lecture of the British Atherosclerosis Society. In 2016, he received the outstanding achievement award of the ESC, in recognition of his overall contribution to cardiovascular science. He routinely gives invited lectures in the most prestigious international scientific meetings like the scientific sessions of the American Heart Association, the ESC, and others. He is also an associate editor of Cardiovascular Research, the British Journal of Pharmacology and the Hellenic Journal of Cardiology. He is board member of the British Atherosclerosis Society and one of the founders of the Scientists of Tomorrow of the ESC’s council on Basic Cardiovascular Science.
Professor Dr Vassilios Vassilikos

Director of the 3rd Cardiology University Department at Hippokrateio General Hospital, Thessaloniki, Greece

Professor Vassilios Vassilikos completed his medical education in 1983 and obtained his Doctoral Thesis at the Aristotle University of Thessaloniki, Greece in 1989. He was trained in Cardiology in Thessaloniki and UK where he subspecialized in Invasive Cardiology and Electrophysiology at St Bartholomew’s Hospital in London and practiced for several years at the Onassis Cardiothoracic Centre in Athens.

Professor Vassilikos is a Fellow of the American College of Cardiology, the European Society of Cardiology and member of numerous National and International scientific societies.

In 2000 was appointed as a Lecturer at the Aristotle University of Thessaloniki and organized the first invasive electrophysiology and automatic defibrillator implantation program in Northern Greece at the AHEPA University Hospital.

As President of the Hellenic Working Group on Pacing and Electrophysiology, organized the National Registries of Ablations and Devices in Greece under the auspices of the Hellenic Cardiac Society.

He is a committee member of the Working Groups for training in undergraduate and post-graduate Medicine, for the National Guidelines for training in Cardiology and drug prescription on arrhythmias.

Since 2014 is the Director of the 3rd Cardiology University Department at Hippokrateio General Hospital, Thessaloniki where he installed a new, fully equipped Hemodynamic suite and CCU with a “Stavros Niarchos Foundation” grant. In collaboration with the Department of Medical Informatics he developed an ECG signal -analysing platform using wavelet analysis. This method is part of his current research activity, and is used in various groups of patients in order to identify subtle electrophysiological irregularities and their relation with clinical prognosis. He participated in numerous international trials as Primary Investigator.

Professor Vassilikos published extensively and actively participates in local, regional and international scientific meetings.
Associate Professor Dr Konstantinos Toutouzas

*University of Athens*

Dr Konstantinos Toutouzas completed his medical studies at University of Athens Medical School, his residency at the First Department of Cardiology of the University of Athens in Hippokration Hospital and an interventional cardiology fellowship in Centro Cuore Columbus, Milan, Italy. Since 2014 he serves as Associate Professor of Cardiology in the First Department of Cardiology of University of Athens. He has also held a visiting associate professorship in University of Bolton. He is a member of several Greek and international scientific societies, including the Hellenic Society of Cardiology, the European Society of Cardiology (FESC), the European Association of Percutaneous Cardiovascular Intervention (EAPCI) and the Society for Cardiac Angiography and Interventions (SCAI). He has also served as Chairman of the Greek Working Group of Interventional Cardiology. His main clinical interest focuses on the area of Interventional Cardiology. He performs the full range of interventions in coronary circulation including coronary angiography, percutaneous angioplasty and intracoronary imaging techniques (intravascular ultrasound and optical coherence tomography). He also successfully deals with the interventional treatment of structural heart diseases, including transcatheter aortic valve implantation, atrial septal defect, patent foramen ovale and left atrial appendage closure, with the use of dedicated devices. Notably, he is a proctor for Evolute R device and for optical coherence tomography imaging.

He has a rich scientific work. His main research interest focuses on invasive assessment of vulnerable or high-risk plaques, including intravascular ultrasound, thermography and optical coherence tomography, non-invasive detection of vulnerable plaque inflammation by novel imaging modalities and the clinical study of patients with severe aortic valve stenosis, undergoing transcatheter aortic valve implantation. He is an author of more than 250 publications in peer reviewed journals. Finally, Ass. Professor Konstantinos Toutouzas has presented more than 530 abstracts, has given more than 80 invited lectures and chaired in more than 20 lectures in international scientific meetings. He is the editor of two books in Greek language and associate editor of International Journal of Cardiology.
**Professor Dr Stavros Konstantinides**

*Professor for Clinical Trials and Medical Director of the multidisciplinary Center for Thrombosis and Haemostasis (CTH) at the University of Mainz, Germany.*

Dr. Konstantinides is appointed Full Professor for Clinical Trials and Medical Director of the multidisciplinary Center for Thrombosis and Haemostasis (CTH) at the University of Mainz, Germany. The CTH is dedicated to integrated patient care and translational research, and funded by the federal German government. Dr. Konstantinides is also appointed Professor of Cardiology at the Democritus University of Thrace, Greece. He graduated from the Medical School of the Aristotle University in Thessalonica, Greece, in 1987. He then completed his clinical training in Cardiology and defended his doctoral thesis at the University of Freiburg Germany. He has worked as consultant cardiologist, Assistant and Associate Professor of Medicine at the Universities of Freiburg and Goettingen, Germany, and as a research associate and visiting professor at the Department of Vascular Biology, the Scripps Research Institute, La Jolla, CA, USA. For the past 27 years, his research has been focusing on basic mechanisms of thrombosis, and on the risk stratification and risk-adapted antithrombotic management of venous thromboembolism. He has published 230 papers in peer-reviewed journals with a cumulative impact factor of almost 1,100, an h-index of 44, over 10,000 personal citations, and 25 book chapters. He has designed and coordinated, and/or has been principal investigator of several high-impact national and international multicenter trials, 7 of which have been published in the New England Journal of Medicine. His research has funded by national and European peer reviewed granting agencies. He is leading member of national and European committees, guidelines task forces and networks focusing on the pulmonary circulation and right ventricular function.
Dr George K. Andrikopoulos
Henry Dunant Hospital director of the 1st department of Cardiology and director of the department of Electrophysiology and Pacing

Dr George Andrikopoulos obtained his medical diploma from the Medical School of Athens University (1990) and his basic training as a Cardiologist at Hippokration Hospital in Athens (1999). As a research fellow of the European Society of Cardiology he was trained on cardiovascular genetics at the Department of Biological Sciences, University of Warwick, UK (2000) and as a Clinical Research Fellow at Walsgrave Hospital, Coventry, UK (1999). He received his PhD at Cardiovascular genetics from the University of Athens (2004).
He is president of the Institute for the Study and Education on Thrombosis and Antithrombotic Therapy (2016), member of the board and founding member of the Hellenic Cardiovascular Research society (2007) and special scientific advisor of the board of the Hellenic Heart Foundation. Regarding his research activities he has published 124 manuscripts cited at Pubmed and a total of more than 300 papers. He was National coordinator of the EuroHeart project and member of the board for WP5 (2007-2009), National coordinator of the CHOB project of the European Heart Network (2004-2006), Principal investigator of the GEMIG, HELIOS, RHYTHMOS, TARGET, MANAGE-AF, PHAETHON, and other studies and co-principal investigator of the multicentre, international, SPICE study.
He works at Henry Dunant Hospital as a director of the 1st department of Cardiology and director of the department of Electrophysiology and Pacing.

44
Speakers CVs

Speakers CVs
After graduating from Medical School in Austria she started residency in general surgery and continued by training with residency in cardiac surgery. Her training was accomplished both in Austria and the United States at Harvard Medical School affiliated hospitals. Since 2003, she has been on staff at Boston Children’s Hospital in the Department of Cardiac Surgery and as faculty member of the Department of Surgery at Harvard Medical School. Dr Ingeborg lead her own research group and has teaching commitments not only at Harvard Medical School and Harvard School of Public Health but also at selected academic institutions in Europe, including European University Cyprus. Combining her medical background with scientific interests, has enabled her to establish novel therapeutic approaches addressing unmet needs in the treatment of congenital heart disease. Longstanding interest in heart failure, has led to the discovery of mitochondria as key players early in disease progression. Hypertrophy is one of the most common causes of heart failure in children and adults. In several of her publications she has established similarities, but also divergent pathways regulating left versus right ventricular hypertrophy. More detailed analysis of the divergent pathways was performed to identify clinically relevant chamber-specific therapeutic interventions which are currently not available. The specific and unique role of mitochondria in this process were early on apparent which led her to further concentrate on this topic. In collaboration with several colleagues at Boston Children’s Hospital Dr Ingeborg established mitochondrial transplantation as novel therapeutic approach for treatment of cardiac diseases including heart failure. First clinical data indicated the success of her approach.
Dr Demetris Papamichael

Director of Medical Oncology at the Cyprus Oncology Centre in Nicosia

Demetris Papamichael is Director of Medical Oncology at the Cyprus Oncology Centre in Nicosia, a post he has held since 1999. He obtained his medical degree from Charing Cross and Westminster Medical School, University of London in 1988. Dr Papamichael trained in internal medicine and obtained his Membership of the Royal Colleges of Physicians (MRCP) in 1992. His subsequent training in medical oncology was completed at the Royal Marsden and St Bartholomew’s Hospitals in London. He became a Fellow of the Royal College (FRCP) in 2002. Dr Papamichael is an American Society of Clinical Oncology (ASCO) Merit Award winner. He is an active researcher and has participated in a number of Industry sponsored studies as well as clinical trials coordinated by the European Organization for Research and Treatment of Cancer and the UK Medical Research Council/National Cancer Research Institute (MRC/NCRI). In addition, he is involved in translational research projects in colorectal cancer.

Dr Papamichael's main clinical interests include gastrointestinal cancer, and cancer in the elderly. He has published his work in a number of peer-reviewed international journals. Dr Papamichael is actively involved in the teaching and organization of courses run by the European School of Oncology (ESO) and is an ESO core faculty member. He is a member of ASCO, the European Society of Medical Oncology (ESMO), and the International Society of Geriatric Oncology (SIOG). Recently, he headed a Task Force responsible for developing recommendations for the management colorectal cancer in the elderly under the auspices of SIOG. He is also a member of the ESMO GI Faculty as well as an ESMO officer.
Professor Dr Gerry Melino
University of Rome Tor Vergata, Italy; Oxford University, London, UK

Professor Gerry Melino currently works as Department Director and Professor of Molecular Biology at the University of Rome “Tor Vergata” in Italy (Email: melino@uniroma2.it). He is also Programme Leader for the Medical Research Council (MRC) Toxicology Unit, in Leicester, UK. His training originated in Italy and in particular Rome, where he obtained his M.D. (1978, University of Rome) followed by clinical specialisations in Paediatrics (1981, University of Rome) and Clinical Oncology (1985, University of Rome). He obtained his Ph.D in 1984 at the University of London in the Chemical Pathology Department, Charing Cross & Westminster Medical School. Upon graduation, he worked as Research Fellow, then Lecturer and later Senior Lecturer (Honorary Consultant) until 1987. Professor Melino returned to Italy in 1988 to the University of Rome as a Lecturer before becoming a full Professor in 1994. Professor Melino has acted as Consultant and Scientific Advisor for several companies and government institutions. He also has significant Editorial activity as Founder and Editor-in-Chief of the Nature-Publishing-Group journals Cell Death and Disease (www.nature.com/cddis) and Cell Death and Differentiation (Impact Factor 9.050. www.nature.com/cdd) as well as serving on the editorial boards of several other scientific journals. The Scientific Interests of Professor Melino are focused on Programmed Cell Death or apoptosis, in neural and epidermal models. Originally, he worked on the Molecular mechanisms of cell death in the skin, a process known as cornification or formation of the cornified envelope. The molecular events were investigated in vitro and in animal models as well as in human genetic pathologies. The role of transglutaminases (type 1, 2, 3, and 5) and their substrates (SPRs, loricrin, keratins) were investigated at biochemical and genetic levels. While still keeping an interest on these aspects, his current work is focused on The p53/p63/p73 family. DNA damage elicit repair mechanisms involving the tumour suppressor gene p53 and the two newer members of the same family: p63 and p73. The molecular events driven by DNA damage to elicit the function of p63/p73 and their transcriptional regulation, is investigated in vitro. The molecular mechanisms of apoptosis and their protein stability and degradation is also under investigation. Transgenic mice and knock-out work for p63 or p73 is in progress.
Associate Professor Dr Konstantinos Dimas
Department of Pharmacology of the Medical School of the University of Thessaly

Dr. Konstantinos Dimas is a Biologist with a Doctorate in Pharmacology from the Medical School of the University of Ioannina. Since March 2011 he serves as Assistant Professor at the Department of Pharmacology of the Medical School of the University of Thessaly. Prior to this position, he was a researcher at the Pharmacology Lab of the Academy of Athens’s Medical Research Institute since 2003. He was the recipient of a Special Education Award (STA) by the International Organization for Research on Cancer (IARC, Molecular Carcinogenesis Unit), a member of the World Health Organization (WHO) where he remained for the period from October 2001 to December 2002. He has and is collaborating with various universities, research institutes and biotech companies in Greece and abroad. At the Department of Pharmacology of the Medical School of the University of Thessaly (where he serves at various positions since 2007) performs research with his group (the Group of Cancer Biology and Therapy) on the study and development of new anticancer therapeutic approaches, such as putative anticancer small molecules, new inhibitors of kinases p90 ribosomal S6 and novel ligands of sigma receptors. Also he and his group work on the development of new and improved animal models of cancer (such as patient derived tumor xenografts in immunodeficient mice). Recently and in cooperation with the US National Cancer Institute (NCI, NIH, Frederick, MD, USA) his interests expanded to the role of the immune system in the development of new cancer therapies (immunotherapy of cancer).
Professor Dr Anastasis Stephanou
Professor of Cell, Molecular Biology and Genetics at the European University, School of Medicine

Professor Stephanou is currently Professor of Cell and Molecular Biology at the European University, School of Medicine (2014 – present). He completed his PhD at the Westminster and Charing Cross Medical School, University of London in 1992. He then did his Post-doctoral training (1992-1995) in the Department of Endocrinology, Cincinnati Children's Hospital, USA, working transcriptional gene regulation. In 1995, he moved as a postdoctoral fellow to the laboratory at the Windeyer Institute of Medical Sciences, UCL where he studied the regulation of heat shock proteins and their cytoprotective properties. During his postdoctoral work, he developed his interest in the Signal Transducers and Activators of Transcription (STATs) factors as key regulators of apoptosis. In 2002, Dr Stephanou became a Lecturer at UCL and in 2005 was promoted to a Reader/Associate Professor. His main research interests is in the field of signal transduction in pathways and mechanisms of cell death (apoptosis), cell cycle regulation and autophagy in disease models such as myocardial infarction injury and also in cancer. Other interests include collaborating with a colleague in the Mechanical Engineering Department at UCL, who has developed a novel technique called bio-electrospraying (BES) for deposition and Other controlled jetting of primary neonatal cardiac myocytes, primary cardiac and endothelial cells, as well as creating a beating cardiac tissue graft and are hoping to use such protocols for transplantation and treatment of severe heart failure models. He has recently edited a book entitled “JAK-STAT Pathway in Diseases” and also in 2012 became Editor-In-Chief of the journal JAK-STAT. He has authored over 150 peer-reviewed articles.
**Associate Professor Dr Andreas Hadjisavvas**

*The Cyprus Institute of Neurology and Genetics - Cyprus School of Molecular Medicine*

Dr Andreas Hadjisavvas is a PhD holder in Molecular Genetics. He holds the position of a Scientist (second to the head) of the department of Electron Microscopy/Molecular Pathology, at The Cyprus Institute of Neurology and Genetics (CING).

He is an Associate professor at the Cyprus School of Molecular Medicine, at The Cyprus Institute of Neurology and Genetics.

He has substantial experience in the application of Molecular Genetics as a diagnostic tool in Cancer predisposition, pharmacogenetics as well as for advancing our knowledge on molecular mechanisms that underpin complex diseases. He has more than 60 publications in international peer reviewed journals.
Dr Christiana Neophytou

Post Doc University of Cyprus

Dr Christiana Neophytou obtained a B.Sc. in Biology from the University of Athens in 2008 and an M.Sc. in Experimental Molecular Biology from the University of Cyprus in 2009. During her undergraduate degree, she investigated the molecular mechanisms induced by environmental chemicals thought to be responsible for carcinogenesis in breast and lung epithelial cells. As part of her M.Sc. degree, she investigated the ability of several natural and synthetic compounds to induce apoptosis in prostate cancer cells, in a collaborative project with Yasoo Health Inc. She obtained her PhD investigating the “Anti-cancer effects of a novel Vitamin E synthetic derivative in breast cancer” from the University of Cyprus in 2014 where she continues working as a postdoctoral research scientist.

Her major research focus during her work in Dr. Andreas Constantinou’s lab at the UCY was to better understand some of the key molecular events that contribute to tumorigenesis and malignant progression, as well as the anti-cancer mechanism of action of novel therapeutic agents in breast and leukemic cancers. In addition, she participated in the FP7 program “GRANATUM” that aimed to identify natural plant-based compounds (using in silico high-throughput screening) that favorably interact with Estrogen Receptor alpha (ERα) and Estrogen Receptor beta (ERβ). Currently she is involved in the Horizon2020 funded “European Human Biomonitoring Initiative” that aims to understand human exposure to chemicals and resulting health impacts. Furthermore, Dr Neophytou collaborates with Dr. Panos Papageorgis, Assistant Professor at the European University. Their research work involves the discovery of critical mediators of breast cancer metastasis which could also represent feasible targets for therapy. They discovered that IL13Ra2, a high-affinity receptor for binding and internalization of IL-13, is a potent driver of breast cancer metastasis.

During her graduate school career, she received several awards and had the opportunity to present her work in internationally recognized conferences, such as the American Association for Cancer Research. She has also acquired considerable teaching experience, by serving as a teaching assistant for three undergraduate courses including the Laboratory Methods and Techniques course, the Molecular Oncology course and the Biochemistry course, as well as by training and supervising several undergraduate, master’s and PhD students. She has published 5 original, 3 review, 2 conference peer-reviewed papers and a book chapter.
Assistant Professor Dr Yiorgos Apidianakis

University of Cyprus

Yiorgos Apidianakis, PhD, has been trained for 10 years at Harvard Medical School in Biomedical Research. He worked for 6 years as a postdoctoral fellow and 4 years as an Instructor in Medicine in the field of human infectious diseases, practicing his research at the Massachusetts General Hospital and the Shriners Hospitals for Children in Boston, USA. He is an expert in modeling human infectious diseases and carcinogenesis in model organisms using Drosophila and mice for preclinical trials (Apidianakis and Rahme Nat. Protoc. 2009; Apidianakis et al PNAS 2009; Bangi et al EMBO Rep 2012). He extends the findings of his team with the use and analysis of human samples from clinical studies. For example, he has found that the Drosophila detoxification gene Glutathione S-transferase S1 (GstS1) and its mouse and human analog (GSTA4) contribute to host defence against infection with the human opportunistic pathogen Pseudomonas aeruginosa (Apidianakis et al PNAS 2005; Apidianakis et al PLoS One 2007; Apidianakis et al FASEB J. 2012). At the University of Cyprus he leads “The Cyprus Intestinal Health Study” (National Bioethics Committee Licence Number: EEBK/ΕΠ/2015/38) a translational to clinical study to explore primarily the effect of regenerative inflammation in colon cancer (Panayidou and Apidianakis Pathogens 2013; Panagi et al Oncotarget 2015; Apidianakis and Iliopoulos EMBO Rep 2015).
Professor Dr. Barbara Seliger
Director of the Institute for Medical Immunology at the Martin-Luther-University Halle-Wittenberg, in Halle, Germany

Professor Dr. Barbara Seliger is the Director of the Institute for Medical Immunology at the Martin-Luther-University Halle-Wittenberg, in Halle, Germany, Director of a FOCIS Center of Excellence, member of the World Immunoscore and SITC biomarker initiatives. In addition she is head of the work group for “Tumor immunology” of the German Society of Immunology. Prof. Seliger’s research team studies the molecular events associated with immune escape of tumors, the role of the tumor microenvironment and immune cell subpopulations for tumor development and therapy resistance. One major goal is to understand the molecular mechanisms, by which tumor cells modulate the immune response in order to escape immune surveillance. This includes immune check point pathways and abnormalities of HLA class I and class II antigens as well as of HLA-G. In addition, her laboratory is involved in optimization and monitoring immunotherapies and in the characterization of biomarkers allowing the prediction of their success. Recently, she became interested in the identification, functional characterization and clinical relevance of immune regulatory microRNAs, RNA-binding proteins and their implementation as therapeutic tools as well as in the role of the tumor and immune cell metabolism in immune surveillance and its modulation as novel therapeutic option alone or in combination with targeted or immunotherapies.

She has published more than 245 papers, is member of the Editorial Board of OncoImmunology, Journal of Translational Medicine, Proteomics – Clinical Proteomics, reviewer of many journals and national as well as international grants including EU grants and organizer/co-organizer of national and international workshops and symposia such as a Keystone Symposium in Vancouver, ITOC meetings in Munich and Prague and the yearly “Tumor immunology meets oncology” meeting in Halle. During her scientific life she did win a number of awards including the recent ARF Award of the Qatar Foundation 2015 and the Award for the most innovative research project in the state of Saxonia-Anhalt December 2016.
Dr Licia Rivoltini

Director, Fondazione IRCCS Instituto Nazionale dei Tumori, Milano, Italy;
Head of Immunotherapy of Human Tumors.

Licia Rivoltini, MD, is Head of the Unit of Immunotherapy of Human Tumors at the Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan. She was awarded her medical degree by the University of Milan in 1986, and went on to complete board certification in medical oncology at the same institution. For 4 years (1992-1996) she joined as Research Fogarty Fellow the Lab of Steve Rosenberg at NIH/NCI in Bethesda, USA where she contributed to the discovery of the first tumor antigens recognized by T cells, and set up protocols for the generation of antigen-specific T cell effectors from peripheral blood for adoptive cell transfer. She then returned to INT as staff scientist responsible for the Immunomonitoring and Vaccine Laboratory. Since 2007, she is covering the position of Head of the Immunotherapy of Human Tumors Unit.

Dr Rivoltini’s research focuses on translational studies on the cellular and molecular characterization of tumor/immune cell interactions and dysfunction in human setting. Her work is also aimed at designing and monitoring of clinical trials based on immunomodulation, including cancer vaccines, immune-checkpoint inhibitors and novel drug or metabolic intervention. The studies are performed in melanoma, lung cancer, colon cancer, hepatocellular carcinoma, prostate carcinoma and others. Her group has been the first one to describe the phenotypic and functional/prognostic features of myeloid-derived suppressor cells in cancer patients and the impact that metabolic dysfunctions in tumor microenvironment, such as local acidity, play on specific immunity. Major interest of the team involves tumor exosomes and their protein/genetic content, as conveyor of immunomodulation and potential diagnostic/prognostic markers and therapeutic tool. Dr Rivoltini is committed to understand why the immune system fails in controlling tumor growth and how effective therapies exploiting T cell immunity can be identified for cancer patients. The group is also involved in setting-up standard operating procedures for the harmonized immunomonitoring of cancer patients, through the participation to international proficiency panels, and the development of guidelines for immunity assessment (MIATA).

Dr Rivoltini holds research grants from the Italian Association for Cancer Research, the Italian Ministry of Health, the European Community and US-based Private Foundations, has authored over 170 publications in peer-reviewed journals, and serves as regular reviewer for Cancer Research, the Journal of Immunology, Blood and others. She is Associated Editor of the Journal of Immunotherapy and the Journal for ImmunoTherapy of Cancer, and member of the Scientific Board of the NIBIT (Italian Network for Tumor BiolImmunotherapy) and IMI (Italian Melanoma Intergroup).

Dr Rivoltini is also active member of several scientific societies, including the International Melanoma Working Group, the Society for Melanoma Research, and Society for Immunotherapy of Cancer (SITC). She is also involved in Advisory Boards and in teaching in the field of ImmunOncology.
Professor Dr George P. Chrousos
Professor of Pediatrics and Endocrinology and Chairman of the First Department of Pediatrics at the National and Kapodistrian University of Athens School of Medicine, Athens, Greece

Dr. Chrousos is Professor of Pediatrics and Endocrinology and Chairman of the First Department of Pediatrics at the National and Kapodistrian University of Athens School of Medicine, Athens, Greece, and former Chief of the Pediatric and Reproductive Endocrinology Branch of the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland. Dr. Chrousos holds the UNESCO Chair on Adolescent Health Care, while held the 2011 Distinguished John Kluge Chair on Society and Technology of the US Library of Congress. Dr. Chrousos pioneered studies that elucidated the effects of stress on the organism at the behavioral, neuroendocrine, cellular and molecular levels and made fundamental contributions to the understanding, diagnosis and treatment of pituitary, adrenal and stress-related pathologies, i.e., major depression, obesity/metabolic syndrome, and autoimmune/inflammatory, reproductive and sleep disorders. He made seminal observations in the glucocorticoid signaling system and deciphered some of its key clinical implications. Dr. Chrousos is universally regarded as one of the most prominent paediatricians and endocrinologists. His work has been cited over 120,000 times (H-index >170), making him one of the most cited physician-scientists in both Clinical Medicine and Biology and Biochemistry and the top cited clinical pediatrician or endocrinologist in the world. He has received numerous major awards, including the Fred Conrad Koch Award, the highest award of the US Endocrine Society. He is a member of the Academia Europaea and the US National Academy of Medicine.
Dr. Johnson is Professor of Anatomy at the University of Athens, and is an active adjunct Professor at the European University of Cyprus, Medical School. She was previously Associate Professor of Anatomy-Histology-Embryology at Ioannina University and research associate at the National Institutes of Health (NIH). While at the NIH she had a joint position at the National Institute of Child Health and Human Development and National Institute of Mental Health. Johnson was trained in Functional Neuroanatomy and Neurobiology at Cornell University, Functional Neuroanatomy and Psychoneuroendocrinology at the University of Maryland, and post-doctoral training in Molecular Neuroendocrinology & Chemical Neuroanatomy at the NIH. All levels of her education and training were accomplished with merit scholarships and competitive training grants.

Johnson has focused her research in the field of neurosciences and in particular in areas related to chemical, molecular and functional neuroanatomy. She has extensively studied in the neuroendocrine alterations associated with stress and immune function, including the hypothalamic-pituitary-adrenal axis and glucocorticoid signaling, in both clinical and basic science research projects. The bulk of her studies are marked by both a multi-level (in-vivo, in-situ and in-vitro), as well as a multi-disciplinary approach aimed at addressing the structure and function of the nervous system. The last 15 years she has collaborated closely with orthopaedic surgeons to address issues related to peripheral nerve neurobiology, focusing on issues related to peripheral nerve anatomy, nerve injury, repair and tissue engineering.

She has an outstanding scientific record with over 200 scientific contributions to the international scientific literature where she has distinguished herself in the field. She is on the Editorial Board of core anatomical textbooks. Her published original work as amassed over 5,000 citations. In addition, she has spoken extensively in areas of neuroanatomy and neuroendocrinology. As a result of her experimental studies, she has actively presented in over 180 scientific meetings, with more than 120 invited lectures at meetings and seminars.

Johnson is known for her rigorous teaching program in Anatomy, and has amassed over 200 teaching hrs per term during her tenure in Ioannina. She lectures on all aspects of anatomy to medical students for over 30 years, and spearheaded the curricular reform of the anatomy program at the University of Ioannina. In addition, she has organized and runs in-depth neuroanatomy hands-on course for neurosurgeons and neuroscientists. She has helped develop the careers of several young physicians and basic scientists in the neurosciences. She has trained graduate and post-graduate students using state-of-the-art methodologies ranging from in vivo surgical manipulations and measures, to in vitro (cell cultures), in situ and molecular techniques (in situ hybridization, immunohistochemistry, etc.)
Professor Dr Leondios Kostrikis

University of Cyprus

Leondios Kostrikis is a Professor of Biotechnology and Virology at University of Cyprus, Head of Laboratory of Biotechnology and Molecular Virology and former Vice-Chairperson of the Department of Biological Sciences. He received his B.Sc. (1987), M.Sc. (1989), M.Ph. (1990) and Ph.D. (1993) degrees from New York University, United States. This was followed by post-doctoral research at the Aaron Diamond AIDS Research Center of Rockefeller University (New York) on the molecular virology of human immunodeficiency virus. He joined the faculty of the Aaron Diamond AIDS Research Center as a staff investigator in 1998 and the Rockefeller University as an Assistant Professor in 1999. He moved to Cyprus in 2003, joining the University of Cyprus. He was a Fulbright Scholar (US Fulbright Commission) and has held fellowship awards from the Elizabeth Glazer Pediatric AIDS Foundation and the Aaron Diamond Foundation, United States. He has directed over twenty research grants from the US National Institutes of Health (NIH), the European Commission, the Cyprus Research Foundation (CRF) and international charitable foundations. He is an Editorial Board member for twelve international journals, and has served on study sections and committees for European and international grant agencies and charities. He is a founder and a former member of the Board of Directors of the European Society for Antiviral Research (ESAR). For the last 20 years his laboratory has made important contributions to the study of human genetics in the transmission of HIV-1 and disease progression, the worldwide molecular epidemiology of HIV-1 infection, and the transmission of HIV-1 drug resistance. Dr. Kostrikis has now turned his attention to novel concepts in HIV vaccine development and prevention of HIV-1 transmission.
Dr. Florian Graedler

*Satellite Speaker for Scientronics*

*Senior Product Specialist Distributors EMEA, in Illumina Inc.*

Dr. Florian Graedler studied Chemistry at the University of Regensburg, Germany and has an M.Sc. in Analytical Chemistry. After working at the Ecole Polytechnique Federal de Lausanne he went to Munich for a PhD project at the Institute of Experimental Genetics at the Helmholtz Society. From there he went to work for 2 years at the European Headquarters of Affymetrix in UK, before joining Illumina as Application Scientist in 2006. Since 2013 he supports the Illumina sales and marketing organization for channel partners in the EMEA region.
Short CV for Introduction
Prof. Philippos C. Patsalis received his BSc degree in biology from the Aristotelian University of Salonica, Greece and his MA, MPh and PhD degrees in Genetics from the City University of New York, USA. He underwent specialization training in Human Genetics at Memorial Sloan-Kettering Center and post-doctoral training at the Cornell Medical Center in New York, at New York University, Columbia University in New York.
Prof. Philippos Patsalis is currently Distinguished Professor at the Cyprus Institute of Neurology and Genetics and the Cyprus School of Molecular medicine. For the last 25 years, he has worked in the field of human genetics and he have served the community as an active academic, researcher and administrator from different posts. He founded and direct the Cytogenetic and the Translational Genomics Departments at the Cyprus Institute of Neurology and Genetics carrying out diagnostic services and research. He also founded the Cyprus School of Molecular Medicine, where he served as the first Professor and Provost providing postgraduate education.
He also served for 10 years as Chief Executive Medical Director of the Cyprus Institute of Neurology and Genetics, the largest academic, research Institute in Cyprus, and was a founding member and president of the Cyprus Society of Human Genetics. He served as an elected board member of the European Society of Human Genetics and as a member of many national and European committees, boards and councils. He has long scientific collaborations with groups in Lithuania in the area of diagnostics and research and was honour as foreigner member of the Lithuanian Academy of Science. He also had the honour of serving as Minister of Health of Cyprus.
Prof. Philippos Patsalis is a scientist with an international reputation in the field of Human Genetics. He was invited lecturer at more than 200 Universities and conferences around the world and he has obtained more than 40 competitive research grants. He has been appointed on the Editorial Board of many international scientific journals, he is the owner of several patents, he has contributed chapters in nine books and he has published more than 130 original peer review papers in scientific journals including Nature Medicine, Lancet, etc. He is elected as a foreign member of various Scientific Academies, including the Lithuanian Academy of Sciences.
Prof. Patsalis received more than 30 national and international awards, such as the National Research Award, the National Award for Innovation, the US State Department Alumni Award, the Silver Medal of the Cyprus House of Representatives, which is the highest honor of the Parliament of the Republic of Cyprus, and the National Award from the President of the Republic of Cyprus.
Professor Dr Kyproula Christodoulou
The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus.

Professor Kyproula Christodoulou obtained her BSc degree in Genetics from Queen Mary College (1987), her MSc degree in Applied Molecular Biology and Biotechnology from University College London (1988) and her PhD degree in Medical Genetics from Imperial College London (1995). She is employed at the Cyprus Institute of Neurology and Genetics (CING) since 1989 and she is the Founder and Head of the Neurogenetics Department. She is a Fellow of the Academy of Translational Medicine Professionals (FAcadTM) and a European registered Clinical Laboratory Geneticist (ErCLG). She is directing/administrating the Department of Neurogenetics and its diagnostic services, research and educational programmes. She has set up ISO 15189 accredited molecular diagnostic services for a wide range of neurogenetic diseases, a reference service for the Cypriot and neighbouring populations. Through her research activities she mapped several rare disease genes and contributed towards the identification of a number of neurogenetic disease genes. She participated as a principal or co-investigator in a considerable number of research projects with a total funding of over 6.0 million Euro allocated to CING. She has mentored and supervised many MSc and PhD students. She is a Professor and the Coordinator of the Medical Genetics Programme of the Cyprus School of Molecular Medicine. Her current research interests include Translational Neurogenetics, Type 2 Diabetes and Systemic Sclerosis.
Professor Dr Marios Cariolou

The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus; Member of the Cyprus National Bioethics Committee and Chairman of the Cyprus Board of Medically Assisted Reproduction.

Was born in 1957 in Kyrenia, Cyprus, and lived there until 1974. He is married with two daughters. He obtained his Bachelor (1981) and PhD (1985) degrees from the University of Delaware and the University of California, Santa Barbara in the United States, respectively. He worked as a post-doctoral fellow in Cell and Molecular Biology at the California Institute of Technology, Pasadena, U.S.A. (1985-1988) and then as a Research Fellow in Cell Biology at the Baylor College of Medicine, Houston, Texas, U.S.A (1988-1990). In 1991, he returned to Cyprus and was employed by the first Medical Director, Neurologist Lefkos Middleton, at the newly founded Cyprus Institute of Neurology and Genetics (CING) where he established and directs the Department of Cardiovascular Genetics and the Laboratory of Forensic Genetics. In 2012, he became a Professor of the CING Cyprus School of Molecular Medicine. He is a member of the Cyprus National Bioethics Committee and Chairman of the Cyprus Board of Medically Assisted Reproduction.
Professor Dr Alberto Mantovani
Senior toxicologist of the Italian National Health Institute (Istituto Superiore di Sanità –ISS) and also an expert of the European Food Safety Authority


The main topic for his scientific and risk assessment activities are endocrine disrupting chemicals: besides collaborating to OECD and EU activities, he has coordinated the pilot national project on EDC (see the EDC-dedicated ISS website: http://www.iss.it/inte), the project PREVIENI, the first initiative on EDC biomonitoring in Italy (http://www.iss.it/prvn) and the project EDESIA under the EU programme LIFE, to implement a science-based substitution of EDC with safer substances (http://www.iss.it/life). He is currently responsible of the ISS partnership into the Horizon 2020 project Eu-ToxRisk (http://www.eu-toxrisk.eu/) a EU-wide programme driving mechanism-based toxicity testing and risk assessment.
Dr Stavros Charalampous,
President of Cyprus Urological Association. In private practice: founder of the Institute of Fictional & Reconstructive Urology in Limassol, Cyprus

Dr Charalambous is a European Certified Urologist Surgeon and the president of Cyprus Urological Association.

In private practice: founder of the Institute of Fictional & Reconstructive Urology in Limassol, Cyprus. He has worked as a Urologist Surgeon in Greece, Cyprus, the UK and US. Dr. Charalampous is also the President of Urodynamics, Neurourology & Female Urology Section of the Hellenic Urological Association (UNUFU), and board member of the European Society of Female & Functional Society and the Mediterranean Incontinence & Pelvic Floor Society; and a member of the Promotion Incontinence Committee International Continence Society. He has acted as as Executive Director and as a Consultant Urologist for the Mediterranean Continence Foundation. He has worked as Chief Doctor Surgeon of the Urology Clinic in NHS- Greece having worked there from 1984 till 2011. In the same hospital, he was also Head of Female Urology and Urodynamics Department from 2001-2011. He was named Board Certificate Fellow of the European Board of Urology in 1992. His fellowships are numerous, including collaborations with some of the top Urology surgeons worldwide: Fellowship – Urodynamics Southsmead Hospital, Bristol UK, April 1992, Denver, USA, April 1994, Paediatric Urology, Mayo Clinic, Rochester, MN, USA Jan- July 1995, Female Urology Liege, Belgium 2004, Glenmont Ferrand France 2005, Amsterdam 2006, Montpellier 2009 and Live surgery w/s in Ippokratio Hospital Thessaloniki, 2005,2006,2007,2009-2010.

Professor Ioannis S. Patrikios
Chairman and Faculty member of the School of Medicine of the European University of Cyprus

Professor Ioannis S. Patrikios completed his PhD studies in 1994, specialized on Immunology and Lipids/Lipidomics and post-doctoral studies specialization in Medical Biochemistry at the City College of NY, next to the world-known Professor CS Russell. Professor Patrikios went through several different fellowships including research specializations/collaborations with different high reputation institutions including, Mount Sinai NY and was awarded advanced Immunology specialization courses at Scuola Superiore d’Immunologia Ruggero Ceppellini, Italy. He served and continues to serve as a Research Scientific Consultant for Industry and higher education. His broad research interests include studies of new therapeutic approaches of chronic diseases by the use of Systems Medicine, through Systems Biology and Nutritional Systems Biology; Lipid Hemagglutinins, Lectins, Immunology and the use of novel interventions against Metastatic Tumor Cells. As from 2004, Professor Patrikios got involved in the research of innovative, pioneer, holistic therapeutic approaches for chronic multifactorial Neurodegenerative diseases, specifically of Multiple Sclerosis. He is affiliated as a Graduate Studies Mentor with the Institute of Brain Chemistry of London. During the last decade he has obtained many competitive research grants, participated in several different collaborative European scientific research-projects and he organized several large European Consortium Platforms for research and Clinical Trials. His 2002 research findings on the effect of frying oils as human hemagglutinins got an international interest; and have been discussed by several different National Food and Drug Administrations, including UK, and through articles in high impact Magazines such as the New Scientist. He has lately been honored with the tittle of a fellow and member of the advisory board of the Forensic Pathology Academy of London. He has been appointed as a reviewer and editor of several international scientific journals in the field of Medicine, Med-Biochemistry, Pharmaceuticals-Therapeutics and Neurology and as a reviewer for research grants. He is the solid author of University Books in Biochemistry and Medical Biochemistry and he has authored numerous peer reviewed, limited co-authored original publications, in high impact factor scientific journals. Professor Patrikios is a member of several International associations and bodies including Sigma Xi. He is the chief scientific investigator of the team which lately invented and patented the nutraceutical formula PLP10 as a new therapeutic intervention for multiple sclerosis. He is the co-founder and Director of PALUPA Medical Ltd (a research and innovation company), that performed and successfully completed the phase II clinical trial for PLP10. Now he is the scientific coordinator of the “MINERAL” phase III multicenter clinical trial for PLP10. At present he is a Professor, Faculty of Medicine and the Chairman of the School of Medicine of the European University of Cyprus and affiliated as a research collaborator at the Cyprus Institute of Neurology and Genetics.
Professor Dr Nikolaos Grigoriadis
AHEPA University Hospital, Thessaloniki, Greece

Dr Nikolaos Grigoriadis graduated from the Faculty of Medicine of the Aristotle University of Thessaloniki. He did his PhD thesis and residency in Neurology in the same institution. He has been specialized in clinical and experimental Neuroimmunology and CNS immunopathology in a number of research centers and institutions abroad. He is now Professor of Neurology at the Aristotle University of Thessaloniki and Head of the MS Centre and the Laboratory of Experimental Neurology and Neuroimmunology of the B’ Dept of Neurology, AHEPA University Hospital. Professor Grigoriadis is member of various international scientific committees such as the European School of Neuroimmunology, ParadigMS, the subcommittee of ENS for Multiple Sclerosis, the ECTRIMS committee (until 2010), Co-founder and Secretary of the Hellenic Academy of Neuroimmunology. He is Ad Hoc reviewer in more than 32 international scientific journals, co-ordinator in more than 40 multicenter clinical trials for MS and principal investigator in collaborative research projects for cell therapies in CNS autoimmune demyelination. His field of interests are: Neuroimmunology; Multiple sclerosis; experimental models of autoimmune diseases (EAE etc); neurodegeneration; immunomodulation; cell therapies. He has published more than 130 papers in peer reviewed journals, and his current citation index is more than 3500 with an H-index: 30.
Nektarios Tavernarakis is the Chairman of the Board of Directors at the Foundation for Research and Technology-Hellas (FORTH), Research Director at the Institute of Molecular Biology and Biotechnology (IMBB), and Professor of Molecular Systems Biology at the Medical School of the University of Crete, in Heraklion, Greece. He is the Director of the Graduate Program on BioInformatics at the Medical School of the University of Crete, and is also heading the Neurogenetics and Ageing laboratory of IMBB. He is an elected member of the Scientific Council of the European Research Council (ERC), the European Molecular Biology Organization (EMBO), and Academia Europaea. He has also served as the Director of the Institute of Molecular Biology and Biotechnology. He earned his Ph.D. degree at the University of Crete, and trained as a postdoctoral researcher at Rutgers University in New Jersey, USA. His research focuses on the molecular mechanisms of necrotic cell death and neurodegeneration, the interplay between cellular metabolism and ageing, the mechanisms of sensory transduction and integration by the nervous system, and the development of novel genetic tools for biomedical research. He has received several notable scientific prizes, including an innovation-supporting ERC Proof of Concept Grant and two ERC Advanced Investigator Grants (in 2009 and 2016). He is also the recipient of the EMBO Young Investigator award, the Alexander von Humboldt Foundation, Friedrich Wilhelm Bessel research award, the Bodossaki Foundation Scientific Prize for Medicine and Biology, the Empeirikeion Foundation Academic Excellence Prize, the Research Excellence award of the Foundation for Research and Technology-Hellas, the BioMedical Research Award of the Academy of Athens, the Galien Scientific Research Award, the International Human Frontier in Science Program Organization (HFSPO) long-term Postdoctoral Fellowship, and the Dr. Frederick Valergakis Post-Graduate Research Grant Program Academic Achievement Award of the Hellenic University Club of New York.
Professor Dr Georgios M. Hadjigeorgiou  
Professor of Neurology School of Medicine, University of Thessaly, Greece

Professor Georgios M. Hadjigeorgiou was born in 1963 in Nicosia Cyprus. He graduated from the School of Medicine (MD), National & Kapodistrian University of Athens in 1989 from where he also got his Doctoral degree in the year 1998. His postdoctoral training included post-doctoral research fellowships in the University of Milano, and the Columbia University, NY in the field of genetics of metabolic myopathies and mitochondrial encephalomyopathies. After his return in Greece in 2000, he contributed significantly to the establishment of the Laboratory of Neurogenetics, Bioscience Unit, University of Thessaly and basically he was the Greek pioneer in genetic epidemiological studies (mainly in the field of genetic association studies) in neurological diseases. His research activity includes more than 130 PubMed publications and this activity has been recognized in more than 2500 citations. Prof. Hadjigeorgiou has extensive both clinical and research experience and currently he is collaborating with almost all Medical Departments in Greece as well as with leading research centers and study groups abroad; such as NIH / NIA, Columbia NY, Max-Planck Institute Munich, GEO-PD, EURRSSG. He granted financial support for his innovative work/research and for his participation in various research programs including FP7; Greek General Secretariat for research and Technology; Cyprus Research Promotion Foundation; Alzheimer Association USA; PD Foundation, USA. From 2008 to 2012 he was the Director at the Sector of Neurology & Sense Organs, University of Thessaly, Greece. He granted positions such as a member of Genetic Epidemiology for Parkinson’s Disease Consortium (GEO-PD), member in Large of the EURRSSG Executive Committee, head of Laboratory of Neurogenetics, CERTH/CERETETH, Larissa, Greece and member of ECTRIMS. From 2012 till now he is a Professor of Neurology School of Medicine, University of Thessaly, Greece where he serves as a Director of the Department of Neurology. Some of his major scientific achievements include: his work on the first genetic defect of Greek patients with mitochondrial encephalomyopathies and metabolic myopathies; isolation, for the first time at European level, of the gene encoding the debranching enzyme and then identification of 3 novel point mutations in patients with Cori disease; establishment: an active ongoing research project (one of few worldwide) for restless Legs Syndrome (RLS) in uremic patients. Prof. Hadjigeorgiou research team was able to present the first non-pharmacological treatment for RLS in uremic patients; first genetic association studies for Greek patients with neurological diseases and currently he is considered as the Greek leader in the field. Moreover, he performed the first population-based epidemiological study in Greece for neurodegenerative diseases- ongoing; and participated in the study published in JAMA 2006, where α-synuclein promoter region was identified as a susceptibility region for Parkinson's disease. Additionally his research team identified the SCARB2 gene as the possible susceptibility gene for Parkinson's disease and performed the first online network meta-analysis system for randomized clinical trials in MS and the first replication study for Greek MS patients using published data from GWAs.
Professor Dr Savvas Papacostas
The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus; Professor of Neuroscience.

Professor Papacostas completed his medical education at Ohio University, his residency in Neurology and Psychiatry at the University of Rochester, and a fellowship in Clinical Neuropyschology and Epileptology at Columbia University in New York. He is currently Head of the Epilepsy and Behavioral Neurology Clinic of the Cyprus Institute of Neurology & Genetics where he established the Clinical Neurophysiology laboratory, the long term monitoring unit for epileptic seizures and the first Ethics Committee in Cyprus. With the establishment of the Cyprus School of Molecular Medicine, he was appointed Professor of Neuroscience. He has also held a visiting associate professorship at the University of Cyprus in Nicosia and an adjunct associate professorship at the University of Rochester in New York. He has been active in epilepsy research including anti-epileptic drug trials, quality of life in epilepsy issues and has established collaborations with several academic institutions in Cyprus and abroad for the evaluation and surgical cure of epilepsy. He introduced surgical treatments for intractable epilepsy in Cyprus and participated, with intraoperative monitoring, in the first operations performed in Cyprus. Moreover, he performed research on Dementia epidemiology, the psychosocial aspects of the disease, clinical trials for novel medications and conducts studies on animal models of Alzheimer’s disease. He has also performed extensive neurophysiological research on new methodologies for the evaluation of the vestibular system. He is on the list of faculty 1000 of International League Against Epilepsy and has been awarded the distinction of Fellow of the American Academy of Neurology. He published extensively and actively participates in local, regional and international scientific meetings. His book "Madness and leadership: From antiquity to the New Common Era' was published in Sept. 2015
Associate Professor Dr. Dimos D. Mitsikostas
Aeginition Hospital, National & Kapodistrian University of Athens

Prof. Mitsikostas graduated from the Aristotle’s University Medical School, Thessaloniki, Greece, in 1985; five years later he obtained his PhD degree in experimental neuropharmacology, from the National & Kapodistrian University, Athens, Greece. He certified in Neurology, in 1993, after he fulfilled the 4-year residency in Neurology Department, Aeginition Hospital, National & Kapodistrian University, Athens, Greece. He has performed post-doc studies in experimental molecular pharmacology of pain in Harvard Medical School, Boston, Massachusetts, USA (1996-1998, Professor’s M.A. Moskowitz laboratory) and in the Institute of Neurology, University College London, London, UK (2000-2001, Professors’ P.J. Goadsby laboratory and headache clinic). As active officer of the Hellenic Navy he served and directed the Neurology Department of the Athens Naval Hospital from 2001 until May 2016. As Associate Professor of Neurology he serves at Aeginition Hospital, heading the Headache Unit, the MS Unit, the Clinical Trials Unit and the Stroke Unit of the 1st Neurology Department. He teaches medical students, neurology residents and fellows. His clinical work is focused on Headache, Multiple Sclerosis, Pain and Nocebo and he has lectured around the country and internationally on all these fields.

He continues to work on animal models for cephalic pain, animal models for Multiple Sclerosis, while he participates in multiple multi-center clinical trials. He is author of 85 peer-reviewed papers with more than 5,000 citations (h-index 27), editor/co-editor in eight textbooks and reviewer and/or member of the Advisory Board in numerous peer-reviewed international medical journal including Lancet Neurology, Neurology, Brain, Pain, Cephalalgia, Headache, Journal of Headache and Pain. He is member of several national and international societies covering the field of neurology, headache, multiple sclerosis and pain.

Prof. Mitsikostas is currently Past President of the Executive Board of the European Headache Federation (President 2014-2016) and President of the Hellenic Headache Society (2015-2018).
Professor Dr Achilleas Gravanis,
Professor of Pharmacology, School of Medicine, University of Crete

Achilleas Gravanis, Professor of Pharmacology, School of Medicine, University of Crete, Researcher at the Institute Molecular Biology-Biotechnology, Foundation of Research & Technology-Hellas (IMBB-FORTH). Affiliated Research Professor, Center of Drug Discovery Northeastern University, Collaborating Scientist Emulate, WYSS/Harvard. He served as member of the Fellowships Committee of FEBS and participated as Chairman and member in numerous research committees of the European Union, including the Programme Committee of Framework Programmes FP6 and FP7. He was the Chairman of Biosciences Committee of the Hellenic Research & Technology Council, and a Member of the Board of the Hellenic Agency for Evaluation and Accreditation of Higher Education. He is actually a member of the Scientific Council of the Hellenic Foundation of Research & Innovation. He published more 130 papers PubMed journals (h index: 43, citations: 5,100). He is the co-founder of biotechnology spinoff Bionature EA Ltd (www.bionature.net).
Dr Tassos Georgiou

Director and founder of Ophthalmos Research and Educational Institute

Dr Tassos Georgiou is the director and founder of Ophthalmos Research and Educational Institute in Nicosia, Cyprus. He divides his time between retina research and clinical practice in General Ophthalmology with a special emphasis in medical and surgical treatment of diseases of the retina and vitreous. He trained at Leeds University in England and he is a Member of the Royal College of Ophthalmologist.

His lab at Ophthalmos Research and Educational Institute investigates the effects of high doses of omega 3 fatty acids against inherited and acquired ocular disorders. He has recently been able to demonstrate that dietary intake of omega 3 fatty acids at a specific dose so that the blood AA/EPA ratio is within a therapeutic range can protect against macular degenerations and optic neuropathies.

Dr Georgiou has authored peer reviewed research articles, has 2 book chapters and patents for treating retinal diseases, optic nerve diseases and dry eyes with omega 3 fatty acids. He is currently the Principal Investigator of a multicentre phase 2 clinical study in Europe to investigate the effects of omega 3 fatty acids on dry macular degeneration and a multicentre phase 2 clinical study in Europe for Stargardt disease. A phase 3 clinical study is towards the end in USA sponsored by the National Eye Institute to study the effects of the patented omega 3 fatty acid on dry eyes.
Dr Georgios Vrakas  
*Consultant Transplant Surgeon at the Oxford Transplant Centre,  
Oxford University Hospitals, NHS Foundation Trust*

Georgios Vrakas is a Consultant Transplant Surgeon at the Oxford Transplant Centre, Oxford University Hospitals, NHS Foundation Trust. He performs Renal (live donor and cadaveric), Pancreas and Intestinal (Isolated bowel and Modified multivisceral) Transplants. He is part of the Oxford National Organ Retrieval Service team and performs multi-organ retrievals. Georgios is also interested in Renal Auto-transplants following ex vivo resection of complex renal tumors and reconstruction of the remnant kidney, a highly specialized service that he provides for all the UK. His research projects are mainly focused on intestinal and vascularized composite allograft (VCA) transplantation. His studies look into the role of the VCA as a surrogate marker for visceral allograft rejection. In August 2016, Georgios was awarded the “Young Investigator Award” by The Transplantation Society for his research on the development of donor specific antibodies after combined intestinal and vascularized composite allograft transplantation.
QX200 Droplet Digital PCR

IT STARTS WITH A DROPLET AND ENDS IN DISCOVERY.
Abstracts
- Invited Abstracts
- Selected Abstracts
- Poster Abstracts
Educating physicians and scientists for the future
Professor Dr. Lee Hartwell
Arizona State University, USA

During my career, I had to make several key decisions. As an undergraduate - what to study. As a scientist, what to research? And as a medical leader – where to encourage new developments. I will relate the considerations that led me to my decisions. Many of the students here will be challenged by the same questions in their careers. The world is now very different and I would like to think with you about what considerations might guide those decisions for me if I were making them now.

Prevention and Treatment of Ischemic Heart Disease and Atrial Fibrillation Update on the two major causes of death and disability

Dr George K. Andrikopoulos
Director of the 1st department of Cardiology and director of the department of Electrophysiology and Pacing, Henry Dunant Hospital

Ischemic Heart Disease (IHD) is the leading cause of mortality and disability in the industrialized world. In addition, a dramatic increase of IHD incidence has been observed at the so called developing world during the last decades. Although in most of European countries the incidence of IHD is falling, the prevalence of IHD in the general population is still high mainly due to the increase in life-expectancy and due to the remarkable advances in cardiovascular disease therapeutics which contributed to markedly decreased case fatality of major cardiovascular events. On the other hand, advances on prevention of IHD have been tempered by the accumulation of cardiometabolic risk factors, which increase the prevalence of diabetes, hypertension, and dyslipidemia at the population level. Novel promises from pharmacotherapy to prevent atherosclerosis include a variety of genetic-based therapies, like PCSK9 inhibitors to reduce LDL cholesterol and canakinumab, an anti-inflammatory autoimmune drug, which have been shown to reduce cardiovascular events and improve prognosis of our patients.

Atrial fibrillation is the most prevalent arrhythmia, affecting 3% of the population and up to 15% of the elderly. Atrial fibrillation is the leading cause for hospitalization due to arrhythmia globally and is responsible for 25% of strokes and consequently is a disease of profound socioeconomic importance and an important contributor for increased medical costs. During the last decade, the use of direct oral anticoagulants has substantially improved the management of cardioembolic risk because of atrial fibrillation but advances on pharmacotherapy to
prevent atrial fibrillation have been modest. On the contrary advances on invasive therapy of atrial fibrillation using catheter ablation of atrial fibrillation have improved the management of this disease which has a significant influence not only to life expectancy but also to the quality of life of affected patients.

Flies to Humans - Humans to Flies: A Virtuous Circle of Colorectal Cancer Prevention
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Assist. Professor Yiorgos Apidianakis

The two Nobel prizes in physiology or medicine of 1995 and 2011 establish Drosophila genetics as a significant contributor of genes and signaling pathways relevant to human disease, including innate immunity and cancer. Other than providing clues on mammalian gene homologue function, relatively little attention has been paid on the translational aspect of Drosophila genes, microbes and environmental factors that influence homeostasis and disease. This is particularly important for colorectal cancer (CRC) prevention, for which molecular diagnostic tools are non-existent. While clinical studies provide a wealth of information on genes and microbes linked to inflammatory bowel disease (IBD) and CRC, it is unknown if they can serve as biomarkers in terms of CRC prevention. I will discuss the line of research of our team showing that many biomarkers of intestinal inflammation and CRC in humans may be modeled and mechanistically tested in flies. Vise versa, genes and processes we find in flies to promote tumorigenesis, such as regenerative inflammation and aging-associated DNA damage, may be tested as biomarkers of CRC risk in humans. Thus, modeling human intestinal inflammation and cancer in flies can provide a means to assess causality of conserved genes and microbes that can colonize the fly intestine. Moreover, successful modeling in flies enables the “treatability” of the pertinent biomarkers via dietary, probiotic and pharmacological interventions and may pave the way for clinical trials of treatments that alleviate intestinal inflammation and the risk for CRC. [Kamilari E, Apidianakis Y, Panagi M (2017) Flies to Humans - Humans to Flies: A Virtuous Circle of Colorectal Cancer Prevention. Arch Clin Gastroenterol 3(3): 047-060. DOI: http://doi.org/10.17352/2455-2283.000038]

Keywords: Biomarkers; Drosophila; Human; Model host; Colorectal cancer; Inflammation
Dietary Supplementation in Multiple Sclerosis

Professor Dr David Bates
Emeritus Professor of Neurology, Newcastle University

It is more than 50 years since epidemiologists and pathologists in Europe and North America suggested a relationship between dietary fat, particularly that in animal fat and the saturated fatty acids and the incidence and prevalence of multiple sclerosis. Neuropathologically a relative deficiency of polyunsaturated fatty acids was identified in the demyelinated lesions in brains from people with multiple sclerosis and, more significantly, in the normal appearing white matter from those same brains. The suggestion which followed was that a relative deficiency in polyunsaturated fatty acids in the diet was a predisposing factor to the development of multiple sclerosis and this led to the concept of correcting the presumed deficiency by dietary supplementation with polyunsaturated fatty acids.

The initial concept received some support from animal studies with experimental allergic encephalomyelitis in which there was evidence that both omega-6 polyunsaturated fatty acids and omega-3 polyunsaturated fatty acids could lessen the severity of the immune mediated disease. The relevance of these animal studies is now called into question by better understanding of the nature of the immune response in EAE when compared to MS.

There were several randomised, controlled clinical trials of intervention with polyunsaturated fatty acids during the 1970s and 1980s when the only available measurements of relapse rate, disease progression and activities of daily living provided uncertain and conflicting results. Most studies would be regarded as being too small, they were frequently performed in single centres, and the endpoints were not always appropriate.

Since 2000 there have been a few studies of polyunsaturated fatty acid supplementation which have again provided variable results. The most recent trial of omega-3 polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids on clinical disease activity and the surrogate marker of MRI failed to show benefit. Modern studies are affected by the concomitant use of disease modifying therapies but there is some suggestion that polyunsaturates and antioxidants may affect relapse rate in people with RRMS. Antioxidants alone have been reported to affect progressive MS, both primary and secondary.
The presentation will discuss the early results and the limitations and problems in the design, monitoring and interpretation of trials in multiple sclerosis involving any form of dietary or vitamin supplementation.

References:

Perivascular adipose tissue as a window to the coronaries
Professor Dr Charalambos Antoniades
University of Oxford

Adipose tissue is considered a “biochemical factory”, synthesizing and secreting a wide range of adipocytokines with endocrine and paracrine effects on the vascular wall. Indeed, it is believed that dysfunctional adipose tissue in obesity and insulin resistance, exerts proinflammatory effects on the vascular wall, inducing atherogenesis. However, we have recently demonstrated that adipose tissue in humans, behaves as a recipient of communication signals from the cardiovascular system, and responds by secreting adipokines or cytokines able to act back onto the vascular wall altering vascular disease pathogenesis. Actually, perivascular adipose tissue hosts “defence mechanisms” against vascular oxidation and inflammation, and its cross-talk with the vascular wall is considered part of physiological vascular homeostasis. This dynamic cross-talk between adipose tissue and the vascular wall has been used recently as a model system to a) identify novel therapeutic targets in the prevention and treatment of coronary atherosclerosis and b) develop novel imaging biomarkers enabling the non-invasive early detection of vascular disease in humans. These novel concepts will be discussed in this lecture.
Stress, Genetics, and Epigenetics and Human Evolution and Development
Professor Dr George P. Chrousos
National and Kapodistrian University of Athens, Athens, Greece

Nowadays, we frequently associate the fields of Evolution, aka Genetics, and Phylogeny, and Development, aka Epigenetics, and Ontogeny, and use the abbreviated term Evo-Devo to refer to both fields. The human organism and the societies it forms are complex systems that, given the enormous impact of human cognitive and emotional empathy, should be considered together. As such systems, humans and their societies are in a relatively stable disequilibrium or homeostasis, that is maintained by extrinsic energy. Complex systems respond adaptively to exogenous or endogenous threats, the stressors, and the state of disturbed homeostasis, or stress, represents a condition that has the power to shape the ability of a species or individual to survive and reproduce. Hence, both evolution and development are influenced by stress. Major evolutionary and developmental stressors include starvation, dehydration or hemorrhage, injurious agents, presence of adversaries and tissue injury. We have adapted our physiology and behavior, both as a species and as individuals, to respond to these stressors as successfully as possible. Now, we have the benefit of the stupendous progress in biology and genetics to understand the mechanisms through which our species has evolved by adapting to and surviving through major evolutionary and developmental stressors. These selective pressures explain, to a great extent, the appearance of the modern chronic diseases of humanity, such as obesity, the metabolic syndrome, hypertension, allergies, autoimmune disorders, anxiety, depression, the pain and fatigue syndromes and sociopathic behaviors. The term Epigenesis was first employed by Aristotle to suggest the process of de novo changes in organismal responses to environmental conditions, as opposed to the inner preformation theory of Plato, who had proposed that all developmental processes were predetermined and unfolded over time. The modern definition of Epigenetics was proposed by C. H. Waddington in 1942, as “the causal interactions between genes and their products to bring the phenotype into being”. Even though epigenetics represent acquired properties that are obtained by the organism over its lifetime, i.e., during ontogeny, some may cross generations or even lead to genetically inheritable changes. The epigenetic process is effected by covalent bonds on the DNA without changes in the base sequence of the molecule, post-translational modification of proteins, DNA-binding proteins or protein complexes, miRNAs, piRNAs and other noncoding RNAs, as well as by formation of super-enhancers, which appear to play major organizational roles in tissue differentiation. Methylation vs. demethylation, as well as acetylation vs. deacetylation, of DNA and chromatin proteins represent key molecular changes in epigenesis. Epigenetic functions include embryonic cell differentiation, genomic imprinting, X-chromo-
some inactivation, retrotransposon repression, somatic cell differentiation, immune function, puberty, sexual orientation, right/left handedness, labor and delivery, maternal and perinatal stress, brain plasticity, memory formation and stress-related behaviors. Behavioral disorders, such as depression and schizophrenia, have a strong epigenetic component. We should note that epigenetic control mechanisms evolve, there is a Lamarckian dimension in evolution, and imprints and methylation marks are erased and reestablished de novo stochastically twice, at the gamete and blastocyst stage, in each generation.

The Transition from Acute Pulmonary Embolism to Chronic Thromboembolic Pulmonary Hypertension: Pathophysiology, Clinical Corse, and Implications for Patient Management and Follow-up

Professor Dr Stavros Konstantinides
Professor for Clinical Trials and Medical Director of the multidisciplinary Center for Thrombosis and Haemostasis (CTH) at the University of Mainz, Germany

Acute pulmonary embolism (PE) is a frequent cause of death and serious disability. The risk of PE-associated mortality and morbidity extends far beyond the acute phase of the disease. In earlier follow-up studies, as many as 30% of the patients died during a follow-up period of up to 3 years, and up to 50% of patients continued to complain of dyspnea and/or poor physical performance 6 months to 3 years after the index event. The most feared ‘late sequela’ of PE is chronic thromboembolic pulmonary hypertension (CTEPH), the true incidence of which remains obscure due to the large margin of error in the rates reported by mostly small, single-center studies. Moreover, the functional and hemodynamic changes corresponding to early, possibly reversible stages of CTEPH, have not been systematically investigated. Thus prospective clinical studies are urgently needed in this field. FOCUS, an ongoing prospective multicenter cohort study on the follow-up after acute pulmonary embolism, is prospectively enrolling and systematically following, over a 2-year period and with a standardized comprehensive program of clinical, echocardiographic, functional and laboratory testing, a large multicenter prospective cohort of 1,000 unselected patients (all-comers) with acute symptomatic PE. FOCUS will possess adequate power to provide answers to relevant remaining questions regarding the patients’ long-term morbidity and mortality, and the temporal pattern of post-PE abnormalities. These data will hopefully provide evidence for future guideline recommendations regarding the selection of patients for long-term follow-up after PE, the modalities which this follow-up should include, and the findings that should be interpreted as indicating progressive functional and hemodynamic post-PE impairment, or the development of CTEPH.
The changing landscape of colorectal cancer management

Dr Demetris Papamichael

Director of Medical Oncology at the Cyprus Oncology Centre in Nicosia

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the Western population. New therapies have been developed over the past 15 years; cytotoxic chemotherapy in combination with biological agents have increased survival for patients with metastatic disease from a median of 12 to over 30 months. The overall 5-year survival for many patients with liver-limited metastatic disease on the other hand, has improved dramatically with more aggressive surgical approaches and peri-operative chemotherapy combinations. Accurately selecting such patients for liver resection however, remains a challenge. Novel end points and newer radiological techniques are being developed to help towards better outcomes for such patients. The discussion of all CRC patients in the context of a multi-disciplinary team brings together all relevant specialties and enhances better outcomes.

The recent molecular classification of CRC in the meantime, provides researchers with new insights into the development/pathogenesis of the disease as well as important prognostic and predictive information. Another emerging therapeutic field is that of immunotherapy. Already, patients with a wide variety of malignancies are benefitting from such approaches. It is hoped that these benefits will soon be extended to patients with Gastrointestinal malignancies. It is very likely that over the next few years, patients with CRC will be broken down into smaller subgroups thus benefitting from precision oncology and benefitting from different therapeutic approaches and management plans.

Sigma ligands as potential novel targeted anticancer therapies

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Background: Sigma receptors [sRs] are a relatively novel group of receptors widespread in the
central nervous system [CNS] [1] and in multiple peripheral tissues [2]. They are divided into two subtypes, sigma-1 (s1R) and sigma-2 (s2R) receptor [3] that are distinguished based on their different ligand selectivity patterns and molecular weights [1]. Selective sigma ligands (agonists and antagonists) have been shown to specifically label tumor sites, induce cancer cells to undergo apoptosis and inhibit tumor growth [4]. However the mechanisms of action underlying the anticancer activity of sigma ligands and their signaling pathways are reported to be highly dependent both on the type of the ligand and the type of the tumor [5] they target even though they may share similarities in their receptor binding properties. Aim of this work is to study the expression of sigma ligands and their relation to pancreatic cancer development, their potential as drugs against this cancer using patient derived animal cancer models and to detect common features of the mechanism of action that ligands of the same selectivity may share.

Methods: The expression of the sigma receptors was examined in:
- Pairs of cancer and normal tissue derived from different patients with pancreatic or colorectal cancer
- Pancreatic cancer cell lines (AsPC1, BxPC3, MiaPaca)
- Primary pancreatic cancer cell lines (021013 Attached, 021013 Floating)

Furthermore, pancreatic cell lines (AsPC1, BxPC3) and primary cell lines (021013 Attached, 021013 Floating) were treated with known chemotherapeutic drugs and multiple sigma ligands (agonists and antagonists). The antiproliferative effect of these compounds was studied with In vitro Cancer Screen assay (SRB assay).

Results: Expression of sigma 1 and sigma 2 receptors was observed in all cancer cell lines and tumor tissues. Sigma 2 receptor is highly expressed in cancer compared to adjacent normal tissue. In addition, sigma 2 receptor seems to be overexpressed in cancer compared to sigma 1 receptor. Amongst the sigma ligands that so far have been tested, PB28 and Siramesine found to exhibit the best anticancer activity. Studies to evaluate the potency of those ligands either as single agents or in combination with established drugs in human-to-mouse models of cancer are ongoing.

References:
Neuroanatomy of Stress: Unraveling the Neural Circuits in Stress & Anxiety Disorders

Professor Dr Elizabeth O. Johnson
Department of Anatomy, Laboratory for Education & Research in Neurosciences (LERNs), National & Kapodistrian University of Athens, School of Medicine, Athens, Greece
Adjunct Professor, School of Medicine European University Cyprus

Stress and anxiety disorders demonstrate a lifetime prevalence of close to 30%, making them among the most prevalent mental illnesses of modern society. The high prevalence and negative effects associated with these disorders, underscores the need to delineate the underlying neural mechanisms to facilitate targeted treatment modalities. While the literature on stress and anxiety disorders is relatively extensive, it has been only the last few years that efforts have focused on the underlying neural circuitry. This review aims to identify the primary features of the neuromatrix of the stress circuit in the healthy brain, as well in stress and anxiety disorders. The primary characteristics of the major stress and anxiety disorders, including panic disorder, specific phobia, social anxiety disorder, post-traumatic stress disorder and generalized anxiety disorder, distinguish them along the fear – anxiety continuum, suggesting that their neural circuits may differ. Three primary anatomo-functional nodes appear to comprise the stress and anxiety neural circuitry. These include a limbic identification node, a cortical evaluation node and a cortical modulation node. The identification limbic node consists primarily of the amygdala and insula and serves to register stimuli and initiate the physiologic and behavioral responses, while the interpretation-evaluation node, which consists of the medial prefrontal cortex and anterior cingulate gyrus, functions to evaluate emotion and gate access of stress information to consciousness.

The hippocampus, the primary component of the modulation-regulation node, acts to modulate other cognitive regions and regulate emotion in a context appropriate manner. The over-riding executive region, which exerts deliberate regulation of emotion, appears to be the lateral pre-frontal cortex. Each of these key nodes in the stress and anxiety circuitry has a key player, which comprise an emotional triad and consist of the amygdala, medial prefrontal cortex and ventral hippocampus. Growing wealth of evidence suggests that the function of these key nodes differs in the primary stress and anxiety disorders. Fear disorders, including.
panic disorder and specific phobia show hyperactivity of the core limbic node, while anxiety disorders, such as post-traumatic stress disorder and generalized anxiety disorder show deficient interpretation and modulation nodes. Not only is the brain neuromatrix involved in the stress circuitry complex, but the evidence supports that chronic stress can affect and shift the structure and function of the neural regions involved.

Cardiorenal syndrome: From bench to bedside and back
Professor Dr Gerasimos Filippatos
National and Kapodistrian University of Athens Medical School, Athens, Greece

The majority of heart failure (HF) patients have some degree of renal dysfunction. There is a bidirectional relationship between the heart and the kidneys in HF, the one affecting the function of the other in a vicious circle that promotes syndrome’s deterioration. The failing heart may impair renal function both by “forward” failure (drop in cardiac output) and “backward” failure (increase in central venous pressure) thus decreasing glomerular filtration rate. Inflammatory activation, cell death and drug therapy may also affect renal function. A significant drawback in assessing these patients is the lack of biomarkers providing an accurate and timely estimation of renal function. Worsening renal function in acute HF patients following aggressive diuretic therapy, in particular, seems to confer an adverse prognosis only when not associated with effective decongestion in the context of diuretic resistance. Increasing diuretic dosage, sequential nephron blockade with different diuretic classes and renal replacement therapy with ultrafiltration along with enhancing cardiac performance with inotropes, when indicated, are measures to overcome diuretic resistance. Better understanding of the pathophysiology and the complex interactions will improve management of the syndrome.

From Microarrays to Next Generation Sequencing: The impact of genomics on modern medicine
Dr. Florian Graedler
Senior Product Specialist Distributors EMEA, in Illumina Inc.

In the last decade Illumina developed sequencing by synthesis (SBS) as the leading technology for next generation sequencing that is today providing over 90% of all DNA sequencing data globally. From targeted sequencing of pre-enriched marker regions over metagenomics studies on microbial communities to whole exome and whole genome sequencing of patients in the clinical routine and entire populations – NGS technology is today present not only in all major clinical research centers but also in routine clinical praxis. Rare diseases, that until recently took years to be diagnosed, can now be identified much more rapidly and compared
with similar cases in global databases. This dramatically shortens the long and erratic path to diagnose these rare disorders, relieve patients and their families and can sometimes even indicate a promising treatment strategy. NGS-based tests can not only help to evaluate pre-dispositions for inheritable cardiovascular diseases or cancer, it also is now used to develop non-invasive tests for the early detection of cancer and to predict the chances for treatment success. The same principle is used to sequence fetal DNA in the bloodstream of the mother, which allowed to develop routine assays for non-invasive prenatal testing (NIPT) for embryonic aneuploidy, which can be the cause of Down Syndrome in the case of trisomy-21.

**Regenerating neuroimplants in spinal cord injury**

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Spinal cord injury (SCI), a traumatic disease characterized by a massive degeneration of neural tissue, is recently targeted for combinatory neuroregenerative therapeutic interventions. Our approach focuses on the development of pharmacologically pulsed neuroimplants, using 3D collagen scaffolds hosting Neural Stem Cells (NSCs). We tested 3D matrices either made of pure bovine collagen I (3D-C) or in combination with 8% chondroitin sulphate proteoglycan (3D-CG). We investigated the effects of these scaffolds on NSCs proliferation, differentiation and functionality in culture. Embryonic cortical NSCs were chosen, as they represent a cell population mainly composed of stem and progenitors cells with high proliferative capacity and trileneage differentiation potential. Our findings show that the composition of 3D scaffolds plays a significant functional role: scaffolds with a combined composition (92% collagen/8% chondroitin-6-sulphate) supported NSCs survival and proliferation throughout a time frame of 10 days in vitro whereas pure collagen scaffolds favored the differentiation of the same cells in functional neurons and increase electrophysiological activity. Due to the high efficacy of the 3D-C scaffold to support the functionality of the differentiated NSCs we used this type of culture system for its transplantation in the spinal cord of mice after experimen-
tal SCI, assessing its possible regenerative efficacy. The dorsal column crash mouse model for experimental SCI was used, where both sensory ascending and motor descending pathways are affected, assessing their ladder-walking performance. Our finding show that the treated with the 3D scaffold-NSC group performed better with reduced foot fault score during these 4 weeks of assessment, compared to the untreated, crash group. Interestingly, transplantation of 3D collagen scaffold seeded with NSCs facilitated the development of neural tissue, induced the regeneration capacity at the lesion site and reduce the extended astrogliosis in the lesion area 6-weeks after the experimental spinal cord injury in mice.

Is neurodegeneration an absolutely inflammation-related process in MS?
Professor Dr Nikolaos Grigoriadis
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Multiple Sclerosis (MS) is considered an autoimmune demyelinating disorder of the Central Nervous System (CNS) affecting mostly young people. The clinical process of the disease varies from the relapsing to almost purely progressive forms. Whatever the case might be, the patients may exhibit progression of disability at various time points after the disease initiates. The underlying pathology of the ongoing disability is neurodegeneration characterized by axonal degeneration, loss of dendrites and synapses etc. Currently available treatments aim to control disease activity by interfering with the adaptive immune reaction and concomitant demyelination in the CNS. However, the same drugs may hardly halt the ongoing disability in the long term.

Several factors, either directly or indirectly related to the immune system have been implicated in the ongoing neurodegenerative process. Among them, oxidative stress, mitochondrial injury and subsequent ion channel dysfunction secondary to chronic inflammation seem to have a constant impact on neurons and axons, leading to their demise during progressive MS. The balance between continuous inflammatory stressors and intrinsic buffering mechanisms depends partly on age, sex and genetic factors, which eventually determine the clinical course of MS. Interestingly enough, in an animal model of MS, few molecular targets with proven neuroprotective properties that are separable from their impact on inflammatory responses have been identified; these molecules include CyPD, ASIC1 and TRPM4.

Presumably, the ongoing neurodegeneration may only partly be related to the inflammatory component of the disease. This is probably the reason that treatments aiming to control adaptive immunity activation are not able to protect axons of becoming gradually degenerated.
Diagnosis of muscle diseases in the era of next generation sequencing
Professor Dr. George Hadjigeorgiou
School of Health Sciences, University of Thessaly, Greece

Muscle diseases comprise a large and heterogeneous group of acquired and inherited diseases. For many decades, muscle biopsy was considered as the gold standard laboratory examination for diagnosis of both acquired and inherited muscle diseases. Next generation sequencing (NGS) technologies provide us with the possibility to map entire genomes or exomes at affordable costs and though influence of our daily clinical practice in terms of diagnosis. The application of NGS technologies is transforming the practice of clinical neurogenetics and revolutionizing the approach to heterogeneous hereditary conditions, including muscle diseases. In recent years, cohort studies showed that the overall diagnostic rate of NGS strategies for patients with inherited muscle diseases is higher than the success rate obtained using the traditional approach gene-to-gene approach. Moreover, many experts pointed to the expansion of clinical phenotypes associated with already known disease genes. In the light of the aforementioned progress muscle biopsy is still a gold standard laboratory examination for acquired muscle diseases and for those where NGS failed to identify a causative gene.

Mitochondrial transplantation - a novel therapy for cardiac disease
Ass. Professor Dr Ingeborg Friehs
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Introduction: Heart disease is the leading cause of death for both men and women in the United States. About 5.7 million adults suffer from heart failure due to underlying causes such as ischemia/reperfusion injury or hypertrophy both of which are a direct result of impaired mitochondrial function. We hypothesize that augmentation and replacement of damaged mitochondria would allow for myocardial cell rescue.

Materials and Methods: Methods and procedures have already been established to allow for the isolation of viable, structurally intact, respiration competent, autologous mitochondria, isolated from remote skeletal tissue in a short time-frame of less than 30 minutes. First, internalization of mitochondria was determined in isolated neonatal cardiomyocytes. Secondly, pre-clinical large animal studies in anticipation of use in humans were performed to ascertain safety, efficacy and lack of immunogenic response of mitochondrial transplantation.
Results: In vitro studies showed that mitochondria are internalized and augment ATP levels. Local injection and intracoronary injection of mitochondria showed specific distribution throughout the LV, validated by PET/microCT imaging, with no effect on rhythm, heart rate of pressures. The use of human mitochondria in animals allowed for the differentiation between native animal mitochondria and transplanted human mitochondria based on immune reactivity to a monoclonal anti-human mitochondria antibody on post-mortem histological tissue analysis. Injected mitochondria are taken up by myocardial cells and are present in the myocardium for at least 4 weeks following injection. Furthermore, injected mitochondria did not elicit any immune or inflammatory response.

Conclusion: Mitochondria are therapeutic targets to prevent the development of ventricular failure in response to pathological stimuli. Injection of viable mitochondria provides a safe and robust therapeutic intervention of enhancing mitochondrial function to meet energy needs. At the same time, maintaining mitochondrial function prevents cardiomyocyte loss to apoptosis.

Human identity testing: How “anonymous” can we be?
Professor Dr Marios A. Cariolou
Head of the Department of Cardiovascular Genetics and Director of the Laboratory of Forensic Genetics, The Cyprus School of Molecular Medicine, Cyprus Institute of Neurology and Genetics

Recent advancements in molecular genetic techniques allow the typing of small quantities of DNA. Today, under certain circumstances the DNA can be attributed to a single person. The presentation will describe past, present and future techniques used in forensic genetics for human identification and the implications of new discoveries in this field relating to crime related and missing persons investigations as well as genetic testing in research and disease diagnosis.

Is nanochemoprevention the future of chemoprevention?
Post Doc. Christiana Neophytou
University of Cyprus

In this presentation I will introduce the concept of cancer chemoprevention as originally coined and defined by M. Sporn et al. in 1976. Proof of concept, that chemoprevention is a valid approach for preventing and controlling cancer incidence and progression, was obtained in 1998 with the landmark study of tamoxifen, a synthetic Selective Estrogen Receptor
Modulator (SIRM) that was evaluated in high risk women for breast cancer. In the following years, additional SIRMs and other drug-based or vaccine-based chemopreventive approaches have been attempted and several were stemmed with success in phase III clinical trials and consequently obtained FDA approval for the prevention of various types of cancer. Surprisingly, diet-based chemopreventive agents, despite promising results in preclinical settings and epidemiological studies, failed to show efficacy in phase III clinical trials. Alternative experimental approaches have been introduced, and are currently being used in preclinical studies, with both drug-derived and diet-derived chemopreventive components. These include: (1) identifying cancer preventive agents that have specific molecular or cellular targets, (2) extensive preclinical mechanistic evaluation of agents before clinical trials are instituted, (3) defining biomarkers that can be used as early predictors of efficacy, and (4) since genetic heterogeneity exists between individuals and tumor types, prescribing personalized drug- or diet-derived chemopreventive agents. Emphasis will be given to the concept of nanochemoprevention as introduced by Siddiqui et al. in the landmark study with the green tea bioactive component EGCT. Finally, I will introduce d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E, which I consider as the most promising amphipathic nano-carrier and a powerful tool in the formulation of lipophilic and poorly soluble compounds. The lack of TPGS toxicity in physiological cells, the targeted induction of apoptosis only in certain cancer cell types and its reported ability to overcome multi drug resistance, make TPGS ideal for nanoformulations. Besides improving the compound’s bioavailability, TPGS could produce additive or synergistic chemopreventive effects with the encapsulated component.

HIV Disease: From Biology to Chemotherapeutics and Beyond
Professor Dr Leonidos Kostrikis
Department of Biological Sciences, University of Cyprus

Emerging and re-emerging human viral infectious diseases constitute an ever-increasing public health threat with devastating socioeconomic consequences of global proportions. In the last forty years alone, the humanity witnessed a number of devastating viral epidemics such as the one caused by Human Immunodeficiency Virus (HIV), the virus that causes the Acquired Immunodeficiency Syndrome (AIDS). HIV-1 currently infects significant fractions of the worldwide population and causes chronic disease resulting in a major burden to public health. As a result of basic research on HIV/AIDS, combination antiretroviral drug therapy (CART), has been developed to specifically target HIV-1 with outstanding success, resulting in a dramatic fall of mortality among HIV-1-infected individuals. In spite of the dramatic decrease of AIDS-related
mortality and the significant increase of life-expectancy among HIV-1-infected people, HIV-1 continues to be transmitted around the world even with higher rates in certain geographic regions. The genetic variability of HIV-1 constitutes the most striking challenge in effectively treating HIV-1 infection. Specifically, the accumulation of drug resistant mutations during suboptimal therapy severely affects the clinical benefits of CART, leading to therapy failure and potentially the transmission of drug-resistant HIV-1 strains to newly-infected individuals. Advanced phylogenetic-based analyses of HIV-1 genomic sequences from HIV-1 sequence databases provide detailed knowledge of old and up-to-date HIV-1 transmission dynamics in human populations in different geographic regions which, is important in identifying populations at risk and in designing better intervention strategies including preventive treatment.

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Emerging issues in the assessment of endocrine disrupting chemicals
Professor Dr Alberto Mantovani
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Endocrine disrupting chemicals (EDC) can alter the homeostasis of the endocrine system thereby causing adverse health; due to the critical regulatory role of the endocrine system, the reproductive function as well as pre- and postnatal development are specifically susceptible to EDC. However, scientific evidence has yet to be translated into international guidelines for evaluating a number of critical, but still insufficiently investigated aspects. These include alterations induced in the peripubertal and long-term effects on tissue and organ programming, leading to enhanced predisposition to the development of tumors (e.g., testis and breast), and/or of the metabolic syndrome. A robust and consistent assessment of these effects is of paramount importance to reduce the risks associated with exposure to so many substances with still limited toxicological data or newly introduced into the market. Translation of experimental evidence into novel assays, endpoints and/or biomarkers can receive significant support from the implementation of the Adverse Outcome Pathways network.

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Italian endocrine disrupters website: http://www.iss.it/inte
Mutp53 & TAp73 regulates tumour microenvironment via hypoxia-inducible factor-1α
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TAp73 opposes HIF-1 activity through a non-transcriptional mechanism, thus affecting tumour angiogenesis. TAp73-deficient mice have an increased incidence of spontaneous and chemically induced tumours that also display enhanced vascularisation. Mechanistically, TAp73 interacts with HIF-1α, promoting HIF-1α polyubiquitination and consequent proteasomal degradation. In human lung cancer, TAp73 strongly predicts good patient prognosis, and its expression is associated with low HIF-1 activation and angiogenesis. These findings demonstrate a novel mechanism for HIF-1 regulation and provide an additional explanation for the molecular basis of the growth, progression, and invasiveness of human cancers.

p53 mutants influence the tumour microenvironment by synergistically acting with HIF-1 to promote cancer progression and metastasis. In hypoxic non-small cell lung cancer (NSCLC), p53 mutants exert a gain-of-function (GOF) effect on HIF-1, thus regulating a selective gene expression signature involved in pro-tumourigenic non-cell-autonomous functions. Hypoxia triggers p53 mutant accumulation on specific genomic DNA elements in a HIF-dependent manner, and depletion of p53 mutants impairs the hypoxia-mediated upregulation of extracellular matrix (ECM) components. Hypoxia leads to the formation of a p53 mutant/HIF-1 complex that physically binds to selective DNA response elements. Analysis of clinical NSCLC revealed that expression of an ECM gene signature was highly correlated with hypoxic tumours exclusively in patients carrying p53 mutations and was associated with poor prognosis. Our data reveal a novel GOF effect of p53 mutants in hypoxic tumours and suggest synergistic activities of p53 and HIF-1. These findings have important implications for cancer staging and might provide innovative last-line treatment options for advanced NSCLC.
Nocebo is the antipode of placebo and refers to adverse events a person manifests after receiving placebo. It has received sparse scientific and clinical attention but it has great importance in headache conditions illustrating the power of the human brain. Relevant mechanisms for nocebo contain prior conditioning and suggestions, expectation, anxiety modulation, and relative experiences. Nocebo submits more to the intervention than to the outcome and includes expected adverse events or, less frequently, nonspecific effects that cannot be substantiated referring to pharmacological action of the treatment. Information disclosure for potential side effects can itself contribute to producing adverse events, or detailed and extensive information by physicians can also trigger nocebo adverse events. Like placebo, nocebo shares key functions in pain conditions and headache. One meta-analysis showed that in RCTs for migraine prevention, eight out of 20 patients treated with placebo experience any adverse event and one out of 20 (5%) withdraw treatment because of adverse events. The same picture stands for tension-type headache and cluster headache, although data for these conditions are poor because of the limited number of RCTs. Other meta-analyses of RCTs revealed that nocebo varies significantly among neurological conditions. The percentage of patients who reported at least one adverse event and treated with placebo in RCTs changes from 43% in migraine prevention up to 67% in Parkinson disease and fibromyalgia. Dropout ratio because of adverse events in placebo-treated patients ranges from 2% in multiple sclerosis to almost 10% in Parkinson disease and fibromyalgia. Notably, in RCTs for depression nocebo was not increased, as someone may expect (dropout ratio 4.5%). In clinical practice, nocebo may be more prevalent than in RCTs. These data emphasize the need for minimizing nocebo to the extent possible by educating the patients and treating them appropriately. To capture patients with potential future nocebo responses a specific self-fulfilled questionnaire (Q-No) was evaluated with 71.7% specificity, 67.5% sensitivity, and 42.5% positive predictive value. Neurologists should acknowledge nocebo as a significant cofactor for treatment adherence and failure and plan techniques to border nocebo, such as patients’ education and close follow-up. Positive suggestions and continuous support increase patient’s compliance and decreases nocebo.
Autophagic pathways in health and disease: Mitophagy and neurodegeneration
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Mitochondria, the main energy hub of the cell, are highly dynamic organelles, playing essential roles in fundamental cellular processes. Mitochondrial function impinges on several signalling pathways modulating cellular metabolism, cell survival and healthspan. Maintenance of mitochondrial function and energy homeostasis requires both generation of newly synthesized and elimination of dysfunctional mitochondria. Impaired mitochondrial function and excessive mitochondrial content are major characteristics of ageing and several human pathophysiological conditions, highlighting the pivotal role of the coordination between mitochondrial biogenesis and mitophagy. However, the cellular and molecular underpinnings of mitochondrial mass homeostasis remain obscure. We found that DCT-1, the Caenorhabditis elegans homolog of mammalian BNIP3 and BNIP3L/NIX, is a key mediator of mitophagy promoting longevity under stress. DCT-1 acts downstream of the PINK-1-PDR-1/Parkin pathway and is ubiquitinated upon mitophagy-inducing conditions to mediate the removal of damaged mitochondria. Accumulation of damaged mitochondria triggers SKN-1 activation, which initiates a bipartite retrograde signaling pathway stimulating the coordinated induction of both mitochondrial biogenesis and mitophagy genes. Taken together, our results unravel a homeostatic feedback loop that allows cells to adjust their mitochondrial population in response to environmental and intracellular cues. Age-dependent decline of mitophagy both inhibits removal of dysfunctional or superfluous mitochondria and impairs mitochondrial biogenesis resulting in progressive mitochondrial accretion and consequently, deterioration of cell function.

PUFA and their Biological Effect
Ass. Professor Dr Marios Pantzaris
The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus

In our recent research and clinical activity, with the development and the use of new technologies like lipidomics, we have started understanding better and better the mechanisms responsible for the physiological and pathological lipid metabolism. Especially the study of Omega 3 and 6 (ω3 and ω6) polyunsaturated fatty acids- PUFAs (like EPA -eicosapentaenoic acid, 20:5n-3 and DHA –docosahexaenoic acid, 22:6n-3 but also ARA -arachidonic acid, 20:4n-6) and their
transformation to bioactive lipid mediators like resolvins, protectins and maresins! All these new molecules are lipid metabolism products that contribute substantially in the “return to homeostasis” process and resolution of inflammation. Increased and special synthesis and analogy dietary intake of omega 3 and omega 6 PUFAs can contribute significantly in almost preventing from the progression of various neoplastic diseases, like breast, prostate, colon and renal cancers. Omega 3 and 6 PUFAs can also slow down the evolution and progression of neurodegenerative diseases like Alzheimer, Parkinson, Amyotrophic Lateral Sclerosis, Multiple Sclerosis as well as severe Depression and Bipolar disorder. Probably in some autoimmune disorders too. Finally, taking into account the anti-aggregation activity in platelets' function they can offer cardiovascular ischemic protection (Myocardial Ischemia and Ischemic Stroke). The current knowledge and experience from the use of these molecules urge us to study in more detail to understand more deeply their mode of action and the way they prevent us from various pathological processes.

Sudden unexpected death in epilepsy: The Cyprus experience in comparison with international data

Professor Dr Savvas Papacostas
The Cyprus Institute of Neurology and Genetics-Cyprus School of Molecular Medicine, Cyprus

Sudden unexpected death in epilepsy (SUDEP) affects 0.09-9.3 per 1,000 person-years depending on the population studied and constitutes the most common cause of death in people with epilepsy. This presentation will review epidemiological data of patients with SUDEP, identify possible risk factors in the population of our tertiary referral center and provide a review of the literature.

We performed a systematic review of patients with epilepsy who had died between 1997 and 2012 and identified those whose death circumstances met the definition of SUDEP. Information was collected regarding sex, age, type of seizures, anti-epileptic therapies, and circumstances of death. Ethical approval was obtained from the institutional medical ethics committee.
Four hundred and forty four new patients were diagnosed with epilepsy among referrals to the epilepsy clinic and were followed to the end of the study period. Seven patients, six males, were identified who met criteria for SUDEP. The average age was 30 years. All patients had had either primary or secondary tonic-clonic seizures. Most were on polypharmacy, and two had a Vagus Nerve Stimulator implanted. Most deaths were unwitnessed and nocturnal. The overall incidence rate for SUDEP in this population was 2.13 deaths/1000 person-years. Overall Cumulative Incidence (or lifetime risk) was calculated at 15.76 SUDEP deaths/1,000 patients.

In our series, SUDEP was primarily a nocturnal and unwitnessed event that affected primarily
young males. Among both males and females patients, 36.8% of all deaths were due to SUDEP. The major risk factor identified was the occurrence of generalized tonic-clonic seizures signifying that every effort should be made to control this type of seizures.

**Specific Omega-3, Omega-6 Polyunsaturated Fatty Acids and γ-Tocopherol in the Therapy of Relapsing Multiple Sclerosis, How and Why: the Paradigm of NEUROASPIS® PLP10 Intervention Efficacy**

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Professor Dr Ioannis Patrikios
Chairman, Professor of Medical Biochemistry and Immunology, School of Medicine, EUC

**Introduction:** Multiple sclerosis (MS) treatments are products of reductionism, partially effective with no (re)myelinating/neuroprotective abilities associated with significant side-effects. We aimed to assess whether our novel interventions, formulated based on systems medicine (SM), comprising specific polyunsaturated fatty acids (PUFA) and vitamins reduce disease activity in patients with relapsing remitting (RR) MS who were either treated with disease modifying treatment (DMT) or untreated.

**Methods:** We contacted a 30-month randomized, double-blind, placebo-controlled, proof-of-concept clinical study at the CING. Of a total of 80 patients, 20 were randomly assigned to receive intervention A (docosahexaenoic acid (DHA)/eicosapentaenoic acid (EPA) (3:1 w/w) omega-3, linoleic acid (LA)/gamma(g)-linolenic acid (GLA) (2:1 w/w) omega-6 fatty acids, omega-3/omega-6 (1:1 w/w), other specific PUFA, monounsaturated fatty acids (MUFA), minor quantity of specific saturated fatty acids (SFA), vitamin A and vitamin E), 20 to receive γ-tocopherol, intervention C, 20 to receive the combination of A and C, intervention B (PLP10) and 20 to receive placebo, as an oral solution, once daily. The primary end point was the annualized relapse rate (ARR) and the key secondary end point was the time to disability progression. The red blood cells (RBC) from each patient blood collection sample at every prescheduled assessment were used as the cells of reference; for evaluation of any correlation between possible efficacy and PUFA profile within the RCB membrane. ISRCTN87818535.

**Results:** PLP10 reduced the ARR by 70% (p=0.003), in relation to the baseline ARR and the
placebo increased by 46% (p=0.354). For the primary end point, PLP10 reduced the ARR by 58% (95% CI 0.10 to 0.79, p=0.016) and for the secondary end point, significantly reduced the risk of sustained progression of disability by 86% over the 2-year period (Hr, 0.11; 95% CI 0.01-0.97, p=0.047) vs. placebo. More patients in the PLP10 group (72%) vs. placebo group (20%) were free from new or enlarging T2-weighted lesions on brain MRI scans over the 2-year study. No adverse events were reported. Interventions A and C showed no significant efficacy. The RBC lipid profile was supportive to the reported PLP10 efficacy by the statistically significant increased quantitative content of the aforementioned PUFA within the RBC membrane as well as by the increased significant release of arachidonic acid (inflammation initiator molecule) from the RBC membrane when γ-tocopherol was present (intervention B); supporting the synergistic theory of all PLP10 ingredients for activity.

**Discussion:** PLP10 treatment significantly reduced the ARR, and the risk of sustained disability progression without any adverse or significant side effects. This is the first clinical study of SM approach medical nutrient formula that holds strong promise as an effective treatment for RRMS.

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**The New Generation Non Invasive Prenatal Test**  
**Professor Dr Philippos Patsalis**  
*The Cyprus Institute of Neurology & Genetics-Cyprus School of Molecular Medicine*  
*Founder and CEO, NIPD Genetics*

There is a great need for the development of new generation safe, dynamic, highly accurate, cost effective technologies, which can facilitate the widespread adoption of Non-Invasive Prenatal Testing (NIPT). We hereby present a novel, safe and cost effective assay, called VERACITY, of diagnostic level accuracy for the non-invasive prenatal detection of genetic disorders which overcomes the limitations of current technologies. VERACITY enables the targeted analysis of selected genomic regions at very high sequencing depth, allows extremely high accurate fetal fraction determination and ensures extremely accurate detection of different types of genetic abnormalities located anywhere in the human genome. The analytical performance of the VERACITY assay was evaluated in two blind validation studies exhibiting 100% sensitivity and 100% specificity and correctly classified all trisomy 13, 18, 21 as well as aneuploidies of X and Y chromosomes. The performance of VERACITY was also assessed in a third blind validation study which consisted of 100 twin pregnancies of at least 10 weeks of gestation, including two trisomy 21 cases, one trisomy 18 case and one trisomy 13 case. Using a special fetal fraction estimation algorithm for dichorionic twins and an optimized dichorionic-twin specific aneuploidy detection algorithm we classified correctly all cases with 100% sensitivity and specificity. Further results from our studies also illustrate the feasibility of our novel
targeted technology for the detection of common and rare genetic disorders in cell free DNA from maternal plasma such as deletions, duplications and point mutations. The clinical impact of cell free fetal DNA testing has been significant as indicated by its quick adoption in prenatal care. VERACITY overcomes limitations of current technologies and enables safe, diagnostic level accuracy and cost-effective non-invasive fetal aneuploidy detection of genetic disorders, which is critical for wide-spread adoption of NIPT.

Exploiting myeloid cells as prognostic biomarker and therapeutic target in cancer patients

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It has been known for long time that myeloid cells, in their different cell subsets including monocytes, granulocytes, macrophages and dendritic cells, may provide a key support to tumor growth and development in a immunocompetent host. What is instead emerging only recently is the increasing contribution that the study of myeloid cells may provide to the identification of prognostic biomarkers and therapeutic targets in cancer patients. Within the febrile race to identify criteria for selecting patients responsive or resistant to immunotherapy with immune checkpoint inhibitors, myeloid cells represent a hot field of investigation. The evidence then that cancer-related myeloid cell dysfunctions are a systemic process that can be thus intercepted in the peripheral circulation, makes these cells a perfect sensor of patient immune suppression and potential source of blood tests that could be easily translated into clinical practise.

Myeloid-derived suppressor cells (MDSC) represent a major subset of circulating dysfunctional myeloid cells in cancer patients, playing a crucial role in cancer development, progression and metastatization. Representing immature myeloid precursors mobilized from the bone marrow by soluble or nanoparticle-related factors produced by the tumor, they progressively accumulate in blood of cancer patients in association with disease progression and poor prognosis. Through a large screening of myeloid markers applied to multicolor cytofluorimetry, we recently defined that broad alterations in the frequency of monocytic MDSC, inflammatory monocytes and granulocytic MDSC, are detected in blood of melanoma patients in association with poor prognosis. On the basis of these data, we defined a Myeloid Index Score (MIS) that predicts prognosis and response to therapy (including immune checkpoint inhibitors) in restrospective and prospectively validated settings. We are presently testing whether MIS does indeed reflect the accumulation of myeloid cells at tumor site.

To identify the mechanisms by which MDSC accumulation occurs, we recently defined an
MDSC in vitro model based on the coincubation of normal CD14+ cells with melanoma exosomes (Exo-MDSC). This model likely resembles the process of MDSC genesis in vivo, possibly involving the trafficking of tumor exosomes to the bone marrow and the conditioning of myeloid precursors, with the consequent release and systemic spreading of MDSC. We and others have recently performed studies in murine models clearly showing that melanoma exosomes home to the bone marrow of tumor-bearing mice and induce MDSC accrual and activation. We have also collected evidence that Exo-MDSC highly resembles blood MDSC from melanoma patients, in terms of gene expression profiling, cyto/chemokine secretion and suppressive activity in T cells.

Melanoma exosomes induce MDSC through the direct transfer, from melanoma to CD14+ cells, of a panel of miRs; this process has a clear relevance in vivo, as MDSC-miR result up-regulated in circulating CD14+ cells and plasma of melanoma patients, and in tumor lesions in association with myeloid cell accrual. The silencing of these miRs blocks the protumor and immunosuppressive effect of myeloid cells both in vitro and in murine setting. We are presently using the miR-MDSC model to screen for new MDSC-blocking drugs, that could have a broad application in clinical setting in improving the response of cancer patients to immune checkpoint inhibitors.

Altogether, solid evidence support the protumor and immunosuppressive role of myeloid cells in human cancer, and point to this pathway as a promising source of immune-related prognostic biomarkers and modulating targets in cancers.

**Translational Neurogenetics towards the identification of targets for the development of therapeutic strategies**

**Professor Dr Kyproulou Christodoulou**

*Neurogenetics Department, Cyprus School of Molecular Medicine-The Cyprus Institute of Neurology and Genetics*

Identification of the mutations that are associated with specific genetic diseases has been the aim of many studies since the characterisation of the DNA molecule, hoping for possible treatment after the causative mutation has been identified. The great majority of monogenenic disease genes has thus far been identified, however, despite major advances in the development of various technologies, gene therapy has yet to become a tangible therapeutic approach. The pathogenetic mechanisms have to be elucidated in order to facilitate possible therapeutic protocols, not necessarily targeting the genetic defect as such, but probably other molecules along the deficient pathway.
It has become apparent that neurogenetic diseases such as the ataxias, spastic paraplegias and neuropathies are characterised by vast genetic heterogeneity. Many families remain undiagnosed at the molecular genetic level despite extensive analysis of currently known genes. It is suspected that these remaining families could each harbour a novel disease gene mutation, thus further increasing the genetic heterogeneity of these rare diseases. Currently, next generation sequencing (NGS) facilitates robust identification of the disease causing mutation in familial and sporadic cases within a considerably reduced discovery time. Indeed, the past couple of years have proven these expectations to be realistic with an increasing number of rare and ultra-rare disease genes being identified. This advantage is giving the opportunity to scientists to focus on the functional characterisation of mutations at various levels, in silico, in vitro and in vivo, thus driving innovation towards identification of targets for the development of therapeutic strategies. Functional characterisation of rare disease mutations is going to provide the missing links within the pathogenetic mechanisms and pathways of specific phenotypes. Thus, innovative approaches towards identification of possible therapeutic targets, are currently focusing on rare diseases. Precision medicine is becoming a realistic scenario.

**Immune escape of tumors: Emerging concepts and therapeutic opportunities**

**Professor Dr Barbara Seliger**  
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Tumor cells use different strategy to evade the host’s immune system including the expression of immune suppressive molecules, downregulation of immune stimulating molecules as well as shifting the phenotype and function of normal immune cells to immune suppressive cells. Although immunotherapies, in particular the immune checkpoint blockade, has received considerable attention during the last years tumors employ effective mechanisms to inhibit anti-tumoral immune responses and reduce immunotherapeutic efficacy. Focussing on classical and non-classical HLA class I abnormalities, which were frequently found in tumors of distinct origin leading to T and/or NK cell-mediated immune escape, the undergoing molecular processes are diverse. While structural alterations of HLA class I antigens represent a rare event, HLA class I abnormalities are mainly due to a deregulation of the expression of HLA antigens and/or components of the antigen processing machinery (APM). This could occur at the transcriptional, epigenetic as well as posttranscriptional level. Recently, increasing evidence suggest that also changes in the tumor metabolism and signal transduction pathways contribute to the inhibition of the anti-tumor response. For example, tumor-mediated shifts in
abundant metabolites and accumulation of metabolic waste products result in local immune suppression and/or alter immune modulatory molecules. In addition, oncogenic signaling also negatively interferes with the expression of immune stimulatory molecules, but upregulates immune suppressive factors thereby facilitating tumor progression. Thus, there exists a link of tumor immune escape mechanisms with signal transduction and metabolism, which might facilitate immune evasion. This will be also discussed in the context of immunotherapies, novel concepts and therapeutic opportunities.

Microsurgery in the New Era of Managing Tissue Loss: Past, Present and Future of Replantation and Allotransplantation

Professor Dr Panayotis N Soucacos
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Even though today replantation surgery has become a routine, it still remains a delicate and demanding surgery, which requires adequate expertise in microsurgical techniques. The indications for replantation procedures have been well established including formulated guidelines for digit, hand, upper extremity and lower extremity amputations. For cases that face more complex problems, the surgeon should be aware of other alternative techniques, such as transpositional microsurgery, various other secondary reconstructive procedures, and today the options of allotranplantation and tissue engineering. Although, overall, replantation procedures have been simplified, a second surgical team can save valuable surgical time by harvesting microvenous grafts, performing bone fixation or tendon repair among other things, while the chief surgeon focuses on revascularization. A number of sophisticated post-operative measures are now available to follow the replanted digit and are invaluable for the early identification of complications before they rapidly turn to an irreversible state. None-the-less, the presence of a member of the replantation team with the assistance of a nurse on a 24-hour basis is still widely accepted as the most beneficial means for avoiding an undesirable post-operative course of the replanted digit. Overall, the current aim which underlines the philosophy in digital replantation today is ensuring not only the survival of the finger, but more importantly its functional use as well. Experience dictates that this can be achieved only if the basic principles and indications are adhered to.

Transplantation of a vascularized limb or its components is defined as composite tissue allotransplantation. This new area in surgery has been made possible by the advent of microvascular surgery combined with advances in our knowledge of transplantation immunology. Hand transplants, as a composite tissue allograft, differ from solid organ transplants, since they consist of several types of tissue such as bone, muscle, cartilage, tendon, skin, nerves
and vessels, with different antigenicities. As such, composite tissue allotransplantation (CTA) is faced by three major obstacles. The first obstacle is acute rejection, which is the most frequent complication of allotransplantation. Acute rejection occurs without exception at least once within the first year of transplantation and may lead to early graft loss. The second obstacle is chronic rejection, which is a poorly characterized process that occurs late after allotransplantation. The third obstacle is the necessary chronic immunosuppression, which may lead to drug side effects such as opportunistic infections, malignancies or organ failure. These three issues have dominated the debate in the hand surgery community regarding the life-enhancing benefits and ethics of human hand transplantation. In the modern era of immunosuppression, 24 hands have been transplanted onto 18 recipients to date. The outcomes of this procedure are still being determined. The ethical aspects of using chronic immunosuppression for a condition which is not life-threatening have also been debated in the surgical communities. Consequently, the future of hand transplants and other composite tissue allografts lies in the development of less toxic immunosuppressive drugs and/or safer methods of tolerance induction, such as chimerism.

My Current approach to female urinary incontinence
Dr Stavros Charalampous
European Certified Urological Surgeon

Urinary Incontinence (UI) remains a worldwide problem affecting women of all ages and across different cultures and races and affects the physical, psychosocial, social and economic well-being of affected individuals and their families.

According to the International Continence Society (ICS) the definition of urinary incontinence (UI) is ‘the complaint of any involuntary leakage of urine.’ The prevalence of UI increases with age, with a typical rate in young adults of 20–30%, a peak around middle age (prevalence 30–40%) and a steady increase in old age (prevalence 30–50%)

According to the 2010 International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report, 1. stress urinary incontinence is defined as voluntary loss of urine on effort, physical exertion, or on sneezing or coughing. 2 Urgency incontinence is part of a larger symptom complex known as overactive bladder syndrome, which is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence.

Urinary incontinence affects a large number of women and results in a substantial socioeconomic burden. Although it is not a life-threatening condition, urinary incontinence has a physical and psychological affect on the patient’s quality of life.
Many minimally invasive and efficacious treatment options are available for both stress and urgency urinary incontinence. Mid-urethral mesh slings for stress urinary incontinence have an acceptably low complication rate with durable efficacy. Newer treatments for overactive bladder syndrome and urgency urinary incontinence, including b-3 adrenergic agonist and intravesical botulinum injection, have greatly changed the landscape of treatment, providing a wide range of treatment options to patients with overactive bladder syndrome that is refractory to traditional anticholinergic drugs.

Annonaceous Acetogenins Promote Cell Death in Cancer cells by Targeting both Na+/K+ ATPase and SERCA ATPase Pumps
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The leaves of Annona muricata, commonly known as Graviola, are known to be rich in flavonoids as well as annonaceous acetogenins. Graviola extracts have previously been shown to have anti-cancer activity. The precise target of action for these plant-base anti-cancer agents is unclear. Recently, using an in silico approach, we showed that the active agent acetogenins of Graviola is a novel target for inhibiting Na+/K+ ATPase and SERCA ATPase Pumps. In the present study we demonstrate that that acetogenins are able to promote cell death in a variety of cancer cell lines but not in non-transformed cells. Moreover, specific inhibitors to Na+/K+ ATPase and SERCA ATPase Pumps were shown to induce cell death in cancer cells but had little toxic effect on normal cells. Finally, using an in vivo xenograft model, Graviola acetogenins was able to reduce the tumour size/volume. The present data indicates that acetogenins are able to promote cell death by targeting and inhibiting Na+/K+ ATPase and SERCA ATPase Pumps and therefore may be potential therapies for the treatment and prevention of cancers.

Therapeutic potential of omega 3 fatty acid supplementation in Macular Degenerations
Dr Tassos Georgiou
Director and founder of Ophthalmos Research and Educational Institute

Macular degenerations contribute a substantial burden to society and healthcare systems as the primary cause of blinding diseases and low vision. There is no effective treatment available
that stops progression or improves vision in patients with macular degenerations.

Dry Macular Degeneration accounts for 80% of all moderate to advanced form to the disease. Its Juvenile form is called Stargardt disease, and it is the most common inherited macular dystrophy in children. It typically presents during the first two decades of life and it often progresses to legal blindness.

Dry Macular Degeneration and its juvenile form occur due to the accumulation of oxidised lipoproteins (A2E) and free radicals in the retina and the choroid of the eye. This accumulation results in oxidative stress and a decrease in the number of retinal pigment epithelium (RPE) and photoreceptor cells, which leads to blurring of central vision and eventually blindness.

Dr Georgiou and his research team at Ophthalmos Institute have performed scientific research on established murine models of several ocular pathologies to confirm the efficacy of ω3-PUFA treatment. These data provide insight into the neuroprotective role of ω3-PUFAs against Retinal Ganglion Cells and photoreceptor damage. Results obtained from a preclinical study indicated not only a protective effect of 3-month administration of ω3-PUFAs, against photoreceptors’ loss in the CCL2-/- mouse model of dry Macular Degeneration but also a regenerative potential on photoreceptor cells. In a Stargardt mice model treated with ω3-PUFAs for 3 months results have shown significant reduction of A2E levels in the retina and significant reduction of lipofuscins in the RPE cells. The importance of assessing AA/EPA blood ratio (when ≤ 2) was emphasised in all these studies in order for the dosage of ω3-PUFAs to be adjusted with the aim to provide the maximum therapeutic effect.

New advances in percutaneous treatment of aortic and mitral valve

Ass Professor Dr Konstantinos Toutouzas
University of Athens

Valvular heart disease is an important cause of cardiovascular morbidity and mortality worldwide. In many countries, though improved living conditions and better access to antibiotics and healthcare have seen a decline in rheumatic heart disease, the prevalence of degenerative valve disease has escalated with ageing of the population. In addition, the number of long-term survivors of surgery for congenital cardiac malformations is growing, with these patients frequently affected by valve dysfunction in later life.

Mitral valve disease affects more than 4 million people in the United States. The gold standard of treatment in these patients is surgical repair or replacement of the valve with a prosthesis. The MitraClip (Abbott Vascular, Menlo Park, CA) is a new technology, which offers an alternative to open surgical repair or replacement via a minimally invasive route.
Aortic valve replacement (AVR) is the second most common cardiac procedure, and aortic stenosis (AS) is the most common valve disease. Population ageing is affecting many countries and is seen as the main driver for the increased incidence of AS in the Western world. AVR is indicated in symptomatic patients with severe stenosis (mean pressure gradient of at least 40 mmHg or maximum velocity of at least 4 m/s) or in asymptomatic patients with impaired left ventricular ejection fraction or low surgical risk. Until recently, standard AVR (SAVR) was the only curative treatment available and formed the backbone of management for most patients. With the recent publication of the Cavalier trial of a sutureless aortic valve and the Placement of Aortic Transcatheter Valve (PARTNER) 2 randomised controlled trial, an updated review of AVR is warranted.

**Left Ventricular Ejection Fraction: An Index of Left Ventricular Systolic Function?**

Professor Dr Filippos K. Triposkiadis  
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The limited myocardial fiber thickening and shortening alone cannot explain the marked left ventricular (LV) volume reduction during LV ejection. This can only be achieved with LV helical (spiral) orientation of the myocardial fibers, which is determined by the non-contractile LV myocardial components (cytoskeleton, extracellular matrix). Preservation of LV ejection fraction (LVEF) in heart failure (HFpEF) is due to the presence of normal ellipsoid LV configuration and spiral myocardial fiber orientation. Conversely, reduction of LVEF in heart failure (HFrEF) results from spherical LV configuration associated with impaired myocardial fiber orientation. Thus, a) LVEF is dependent not only on LV myocardial fiber shortening but LV geometrical factors as well, b) current classification of HF based on LVEF should be revised, and c) future therapy of HF should focus on interventions affecting the non-contractile LV myocardial components rather than on LV myocardial contractility.

**Atrial fibrillation: what do we know and what we can do in 2017?**

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Atrial fibrillation (AF) is the most common tachyarrhythmia, and it is estimated that almost 25% of the middle-aged adults in Europe and US will develop AF. AF prevalence is increased with age, hypertension, valve disease, heart failure, coronary artery disease, obesity, diabetes mellitus and chronic kidney disease. AF is a condition associated with increased all cause mor-
tality (two-fold in women and 1.5 fold in men). Stroke, left ventricular dysfunction, and death related to these pathologies, cognitive decline and vascular dementia, increased hospitalizations and impaired quality of life, are conditions associated with AF.

The underlying pathophysiology varies among different AF types; triggers at the pulmonary vein ostia being the most common in the paroxysmal type in the absence of structural heart disease, and multiple wavelets, nests and rotors associated with abnormal substrate (presence of fibrosis) in patients with structural heart disease. In the recent years there is increased evidence that AF is an expression of an atrial cardiomyopathy, even in the “lone” type.

Important points to consider during the therapeutic approach are the following: understanding the substrate, calculating the thromboembolic risk and stroke prophylaxis, and preventing AF recurrences.

There is increasing evidence that certain types of AF are genetically predisposed. The use of novel techniques (MRI, electro-anatomic mapping, signal analysis using wavelets, etc) has shown the association between the extent of fibrosis, frequency of episodes, clinical type and prognosis of AF.

Anticoagulation is the first line treatment for thromboembolic event prophylaxis in the majority of patients with AF, as assessed by CHADS2VASc score. In the recently published European Society of Cardiology guidelines aspirin is no longer used for thromboembolic prophylaxis in patients without contraindications for anticoagulation. The non-VKA oral anticoagulants (NOACs) are preferred to direct oral antagonists vitamin K antagonists (VKAs), since the former cause significantly less intracranial bleeding compared to the VKAs. In selected patients with increased risk for thromboembolic events, in whom anticoagulation is contraindicated, the left atrial-occluding device can be used.

Rhythm control can be achieved with medical treatment or interventional therapy (ablation or surgery). Ablation has been proven by randomized trials to be superior compared to antiarrhythmic drugs for long-term maintenance of sinus rhythm. Radiofrequency or cryo energies have been used for ablation with similar success rates. In 30-40% of patients a second procedure is required for long-term success. In the initial procedure electric isolation of all pulmonary veins is the target, leaving more complex maneuvers for the redo procedure (i.e. roof or mitral isthmus lines, ganglia etc). Due to the satisfactory results of ablation this can be proposed as the first line treatment option in experienced centers. In Greece, data from the National Ablation Registry show that this procedure is the most common ablation type per-
formed, and the results and complications are similar to those from established, big-volume European or US centers.

Current research is aiming towards the early diagnosis, thromboembolic prophylaxis and treatment of AF, and new technology (including ablation using MRI) is developing for the safer and more successful elimination of AF episodes. The physician should be familiar with all available therapies, assess each patient individually and propose the best available treatment in order to minimize mortality and improve quality of life.

Current Concepts in Transplantation: Combining Vascularized Composite Allografts with Intestinal Transplants

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Introduction: Abdominal wall transplantation (AWTx) offered a potential solution to the often-challenging closure of the abdominal wall at the time of intestinal transplantation (ITx). However, besides facilitating closure, the AWTx has been proven a promising asset for early, patient led rejection monitoring. We have therefore used sentinel skin grafts (SSG) for solely graft monitoring purposes when there was no clinical need for AWTx.

Methods: We performed a retrospective analysis of all patients undergoing intestinal and vascularized composite allograft (VCA) transplantation (AWTx and SSG). Clinical presentation of rejection was correlated with histology, stoma output, citrulline levels and endoscopy findings.

Results: From October 2008 to December 2016, 34 patients underwent ITx in our institute. Ten underwent a modified multivisceral transplant and 24 an isolated small bowel transplant. Mean age was 41.9 years (range 23-73). M/F: 20:14. Median follow up was 774 days (range 16-3029). All patients had Campath induction (30 mg intravenously, 6 hours after reperfusion) followed initially by Tacrolimus monotherapy (trough level of 8-12 ng/ml). Twenty patients received a VCA in addition to ITx. There were 5 intestinal biopsy proven rejections in the IT alone group (36%) and a further 5 patients in the IT group were falsely treated for rejection, as this was later labelled as infection. There were 7 patients with rejection in the VCA part of the IT+ VCA group (7/20, 35%). These patients presented with a rash limited to the VCA. Of those 7 patients, there were 3 with concurrent intestinal rejection (3/20, 15%) with a lead-time of 5-7 days between VCA and IT.
There have been no episodes of intestinal rejection without a preceding VCA rejection.

**Discussion:** We report on a series of combined VCA and ITx. The skin component has been utilized as a visual, dynamic canvas for remote immune monitoring of visceral grafts. It has so far been useful for patient led monitoring of the ITx graft since it is visible and presents the earliest and only sign of rejection.

**Applications of pharmacogenetics; our experience the last six years**

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Pharmacogenetics, the science of how an individual’s genetic makeup influences the response to certain drugs, has improved significantly the decision-making process by providing critical insights into how a patient will react to a specific treatment. During the past few years, new medical treatments known as “targeted therapies” have become available. These have changed dramatically the repertoire of treatment options of non-small-cell lung cancer (NSCLC), colorectal cancer, metastatic melanoma as well as ovarian cancer.

For example results from recent clinical trials show that patients with epidermal EGFR mutation-positive NSCLC, might have a survival advantage over those with EGFR mutation-negative disease. Currently patients diagnosed with lung cancer are better stratified using an integrated approach that includes data from histology, immunohistology and molecular biology. In this context the status for the EGFR status is mandatory, for selecting the more efficacious front line therapy.

Since January 2011, pharmacogenetic tests have become an integral part of contemporary oncology practice in Cyprus. The Department of EM / Molecular Pathology of the Cyprus Institute of Neurology and Genetics is offering genetic testing by examining DNA from tumor biopsies for the EGFR and BRAF genes of lung cancer, BRAF gene for metastatic melanoma, BRAF, KRAS and NRAS genes for colorectal cancer and BRCA1 and BRCA2 genes for ovarian cancer. Over the last six years more than 1200 tumor biopsies have been tested, for the above genes, by the EM/Molecular pathology Department.
The association between brain iron accumulations with blood iron metabolism markers in multiple sclerosis patients

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Background: Multiple studies have previously confirmed the existence of high iron accumulation (HIA) in the brain deep gray matter (DGM) structures of multiple sclerosis (MS) patients. It is thought that HIA may play an important role in MS pathophysiology and its neurodegenerative nature. Nevertheless, the underlying cause of HIA in MS is not understood yet.

Objectives: The aim of this study was to investigate the probable association between blood iron metabolism markers with DGM iron accumulation in MS.

Methods: Based on the study inclusion and exclusion criteria, 30 randomly selected patients with relapsing remitting MS (22 females, 8 males), receiving beta-interferon as disease modifying treatment, were included in the study. Demographic data of patients and data of their MS disease were gathered. Brain iron accumulations in DGM were evaluated by T2 brain mapping method with a 1.5 Tesla MRI machine with standard head coil. The transverse relaxation rate (R2) indices for regions of interests were calculated by ImageJ software (National Institute of Health, USA). Blood samples were taken for measuring red blood cell mass, hemoglobin, serum iron, total iron binding capacity (TIBC) and ferritin. The associations between variables were studied by conducting correlation studies. Statistical analyses were carried out using SPSS software (SPSS Inc., USA). Bonferroni correction method was applied to determine appropriate p-value for each set of multiple correlation tests.

Results: Thirteen patients (11 females) were found to be anemic. Among them, seven cases (all females) had iron deficiency anemia. Among the iron metabolism markers, only TIBC showed significant inverse correlations with the R2 index of Caudate (R=0.61, P<0.0001) and Globus Pallidus (R=0.63, P<0.0001). TIBC was also positively associated with the age of the onset of MS (R=0.61, P<0.0001).

Conclusion: We found that lower levels of TIBC are associated with higher DGM iron accumulation in MS.
and earlier disease onset age. TIBC is an indirect measurement of transferrin function. Transferrin is the main iron transporter in the body. The results suggest that HIA in the brain of MS patients may be due to a dysregulation of iron transport. Further studies are needed to elucidate the cause of these associations. This important finding may shed more light on the complicated pathophysiology of this disease.

SA02 Stroke outcomes in Polish pediatric patients with arterial ischemic stroke depending on gender
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Background: Arterial ischemic stroke (AIS) is a rare, heterogeneous disease in which multiple risk factors, genetic and non-genetic have impact on both, development and the outcome of the disease. AIS is reported to be more frequent in boys, but the explanation of the fact is not clear. Previous data regarding association between 677C>T polymorphism within the gene encoding methylenetetrahydrofolate reductase and AIS showed that carrier-state of T allele also increase the risk of AIS in boys.

The aim of the study was to analyse prevalence of stroke outcomes in dependence of gender in pediatric patients with AIS.

Method: We retrospectively reviewed 78 children <18 years with their first AIS, which was identified by an International Classification of Diseases, Ninth Revision. Children were recruited in the Department of Pediatric Neurology. Statistical analyses were made using Statistica 12.0 software.

Results: We observed, that AIS was more common in boys (57% vs 43% in girls). Age at the time of AIS was comparable between boys and girls. Boys had higher birth weight compared to girls (3186.47g±530.69 vs 2955.60g±514.22,respectively) although the difference were not significant (p=0.094). The total anterior circulation infarct (TACI) stroke was the most frequent stroke subtype in the group of boys (38%) while in girls - lacunar anterior circulation infarct (LACI) stroke subtype (39%). Comparing frequencies of stroke subtypes between boys and girls we observed significantly higher prevalence of posterior circulation infarct (POCI) stroke in the group of boys with AIS (20% vs 3% in girls,p=0.038). The focal cerebral arteriopathy (FCA) of childhood was more common in boys than in girls (67% vs 55%) while heart disease was more prevalent in girls compared to boys (18% vs 16%) however the results were not significant. When we analysed stroke outcomes we found that hemiparesis, epilepsy and intellectual delay were more common in girls (82%, 30%, 12% respectively vs 67%, 22%, 9% in boys, respectively) however not reaching statistical significance. One of the recruited girls died during the follow-up.
Conclusions: The female sex seems to have some impact on worse prognosis of AIS however our observations require confirmation on larger group of patients. The authors declare no conflict of interests.

SA03 Molecular modelling studies on the recently-solved crystal structure of human histone deacetylase 6 (HDAC6) catalytic domain 2 complexed with Known HDAC inhibitors and the design of potential inhibitors for cancer therapy

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Histone deacetylase 6 (HDAC6) is unique among HDACs as it bears 2 homologous catalytic domains (CD1 and CD2). Both catalytic domains may be fully functional and contribute independently to the overall activity of the isoform. Some studies suggested that both HDAC6 catalytic domains were required for full tubulin deacetylase (TDAC) activity while in other study TDAC activity was associated with CD2. Overexpression of HDAC6 in a variety of cancer cell lines and mouse tumor models has been reported. HDAC6 is required for oncogenic transformation and cancer metastasis and therefore a critical target for anticancer drug design and development. Here, with the recently solved crystal structure of HDAC6 CD2 available, the binding modes of the established HDAC inhibitors were assessed by molecular docking and potential inhibitors designed against the enzyme by pharmacophore modelling. The structural dynamics of the ligand-HDAC6 complexes were examined by nanoscale molecular dynamic (MD) simulation. Findings of these study suggested new potential inhibitors of HDAC6. This study may provide insight on the molecular interaction pattern the known and newly-designed inhibitors with HDAC6 CD2, creating avenues for further modelling-based and experimental studies toward the design of potent and selective inhibitor for cancer therapy.

Keywords: HDAC6 CD2, molecular docking, Molecular dynamics simulation HDAC inhibitors, cancer therapy

SA04 Detection of aberrant methylation in Relapsing-Remitting Multiple Sclerosis with MS-MLPA

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OBJECTIVE: Determination of the methylation status of a number of genes in patients with relapsing-remitting MS.

BACKGROUND: Multiple sclerosis (MS) is a complex neurodegenerative disease of the central nervous system. Epigenetic mechanisms may be involved in the development of MS, as the pathophysiology of the disease involves both genetic and environmental factors. DNA methylation, a the best described epigenetic modification, may predispose to MS, as aberrant methylation in the promoter regions across the genome seems to underlie several processes involved in the onset and course of MS.

DESIGN/METHODS: Methylation-specific multiplex ligation dependent probe amplification (MS-MLPA) was used to determine the status of 31 CpG islands located across 8 genes (RUNX3, MLH1, NEUROG1, IGF2, SOCS1, CDKN2A, CACNA1G and CRABP1) in 33 healthy controls and 66 MS patients, 33 of whom in relapse and 33 in remission. Polymerase chain reaction (PCR) amplicons were separated by capillary electrophoresis and were evaluated using Coffalyser software.

RESULTS: The methylation levels in the tested probes ranged from 0% to 31%. Methylation positivity for RUNX3 and CDKN2A differed significantly between MS patients and healthy controls (chi-square test, p=0.017 and p=0.032, respectively). Additionally, maximum methylation in the tested CpG islands across RUNX3 and CDKN2A genes was significantly different between patients and controls (t-test, p=0.021 and p=0.01, respectively). Results from Roc curves demonstrated that the appropriate cut-offs to distinguish patients from healthy controls were 2% for RUNX3 (OR: 3.316, CI: 1.207-9.107, p=0.024) and 3% for CDKN2A (OR: 3.077.CI: 1.281-7.39, p=0.018). No difference in methylation was observed between relapses and remissions in any of the genes.

CONCLUSIONS: Methylation patterns of RUNX3 and CDKN2A genes may be able to distinguish between MS patients and healthy controls, but not between MS patients in relapse and remission. Further studies are needed to confirm if these methylation patterns can serve as important site-specific biomarkers for MS.

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Selected Abstracts

SA05 Specific delivery of therapeutic sequences in muscle by RNA aptamers
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In muscular dystrophies, the necessity for oligonucleotide gene therapies to target several different muscles at once, demands systemic administration. Significant progress has been made with some oligonucleotide chemistries entering the early phases of clinical trials. Recently, chemical modifications such as phosphorodiamidate morpholino and 2′ O-methyl phosphorothioate have been used in clinical trials for Duchenne Muscular Dystrophy. Nevertheless, the therapeutic outcome of any gene therapy approach, not limited to oligonucleotide therapies, depends on selective expression to target tissues. The undesirable distribution to non-target tissues leads to substantial loss of therapeutic molecules with an eventual lower target efficacy. Coupling the molecules with target-specific molecular vehicles could significantly improve tissue specificity and uptake. To address this need, we applied a cell-SELEX (systematic evolution of ligands by exponential enrichment) approach and identified an RNA aptamer that exhibits high affinity and selectivity for skeletal muscle cells. The cell-SELEX approach was driven towards the enrichment of aptamers that internalize into target cells (cell internalization SELEX). We demonstrated that, when applied to skeletal muscle cells in culture, the RNA aptamer has a significantly higher internalization capacity compare to control sequences. We further showed that following internalization, the selected aptamer escapes the endosomal pathway thus allowing efficient translocation to the cytosol. As subsequently shown, this internalization ability is specific for skeletal muscle cells as opposed to other non-target cells. Finally, when tested in vivo, the selected RNA aptamer gains entry in myofibers suggesting a potential new approach for targeting the skeletal muscle. In summary, our study sets a platform for identifying novel RNA aptamers for the delivery of therapeutic oligonucleotides to diseased muscles. Ultimately, this will aid in the development of targeted therapies to combat muscular dystrophies.

Keywords: muscular dystrophy, aptamers, SELEX, delivery, therapy.
SA06 Variations of transverse foramina in cervical vertebrae: what happens to the vertebral artery?

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Purpose: The purpose of this study is to examine variations of the foramen transversarium and the vertebral artery in CT angiographies (CTa) of the cervical spine, investigate their coexistence and present possible considerations regarding such variations in spine surgical procedures.

Methods: Fifty CTa of the neck were retrospectively reviewed. Transverse and anteroposterior diameter of the foramen and diameter of the vertebral artery were measured. Variations of the foramen and the vertebral artery were detected.

Results: Cervical CTa of 32 males and 18 females (mean age: 66.4±10.78 years), all belonging to the Indo-European race, were reviewed. Variations of the foramen transversarium were found in 17 vertebrae (4.85%) of 15 patients (30%). Duplication of the foramen was the most frequent variation, followed by the open foramen, the absence of the foramen, the triple foramen and the hypoplastic foramen. Variations of the vertebral artery were found in 7 patients (14%) and asymmetry was found in 12 (24%) patients. Moreover, 6 patients presented with hypoplastic vertebral arteries (12%). When examining coexistence, 60% of patients exhibiting variations in the transverse foramen, were also exhibiting variations or asymmetry in the vertebral artery, compared to 25.7% of patients with no foramen variations (p=0.02).

Conclusions: Vertebral artery injury is not common but may be a disastrous complication during cervical spine surgery. Proper preoperative planning is essential for any surgeon and exact knowledge of the anatomy in each patient is essential. This study strongly recommends the preoperative use of a CTa when suspicion of a variation is present and implied by a foramen variation.
Selected Abstracts

SA07 Molecular genetic diagnosis of cardiomyopathies by Next Generation Sequencing panel
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Background: Cardiomyopathies are a heterogeneous group of heart muscle disorders, associated with mechanical or electrical abnormalities that may lead to ventricular hypertrophy or dilatation and resulting in structural and functional abnormalities. The cause varies among the different types of cardiomyopathies and frequently has a genetic origin. Cardiomyopathies are classified according to anatomy, structure and physiology into dilated, hypertrophic, restrictive, arrhythmogenic right ventricular, and unclassified. In many cases the phenotype of the patients is not clear and may combine two or more types. Most cardiomyopathies can be inherited; the most common of autosomal dominant inheritance. Today more than 60 genes and 700 mutations have been associated with cardiomyopathies. The goal of this study is to validate an NGS cardiomyopathy panel in order to introduce it for the molecular diagnosis of Cypriot patients.

Materials and methods: We performed NGS cardiomyopathy panel analysis in 11 clinically and molecularly diagnosed cardiomyopathy patients and 7 neurogenetic disease patients.

Results: NGS cardiomyopathy panel analysis confirmed the molecular diagnosis of the cardiomyopathy and neurogenetic disease patients as follows: 4 with PKP2 mutations, 1 with DSP mutations, 2 with DSC2 mutations, 1 with DSC2 and JUP mutations, 1 with DSP and DSC2 mutations, 1 with DSC2 and PKP2 mutations, 3 with LMNA mutations, 2 with a TTR mutation, 1 with a SGCG mutation and 1 with an FXN mutation.

Conclusion: The validation for the correct identification of mutations through NGS cardiomyopathy panel analysis was successful. A new, technologically advanced method was established and validated for the molecular diagnosis of cardiomyopathies.
SA08 FULL GENOME SEQUENCING AND PHYLOGENETIC ANALYSIS OF THE FIRST WEST-NILE VIRUS IDENTIFIED IN CYPRUS

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Introduction: West Nile virus (WNV) is a neurotropic mosquito-borne pathogen belonging to the Flavivirus genus within the Flaviviridae family. The virus is maintained in an enzootic cycle in birds as amplifying hosts by ornithophilic mosquito vectors belonging to the Culex species, but can be transmitted to other mammals including humans serving as dead-end hosts (1,2). WNV is an enveloped single-stranded positive-sense RNA virus of approx. 11kb. Recently, we had reported the first human case of neuroinvasive West-Nile virus infection identified in Cyprus in an elderly non-immunosuppressed patient with a clinical picture of rapidly progressing ascending paralysis mimicking Guillain-Barré syndrome (3). The aim of this study was to establish the complete genomic sequence of the virus found in that patient and to conduct a phylogenetic analysis.

Materials and Methods: Previously, it was shown that Whole Transcriptome Amplification (WTA) techniques, which are based on multiple displacement amplification (MDA) can be successfully used for amplification of RNA virus genomes. Because of the limited amount of viral genomic material available, a similar approach was employed here using the Quantitect Whole Transcriptome Kit (Qiagen) to increase the amount of cDNA necessary for sequencing the complete genome. The successful amplification of the viral RNA was followed by Sanger sequencing of overlapping PCR products. Sequenced amplicons were assembled and phylogenetic analyses were conducted in MEGA6. Full-length alignment of representative WNV isolates was performed using MUSCLE.

Results: The nucleotide sequence of the WNV genome determined in this study has been submitted to GenBank under accession no. MF797870. The sequenced genome comprises 10,982 nucleotides with a polyprotein of 3,434 amino acids being encoded within a single open reading frame. The WNV sequence from Cyprus grouped clearly into genetic lineage 1, clade 1a, cluster 2 having the highest nucleotide identity with a strain isolated from a dromedary camel in the UAE in 2015. Cluster 2 strains have been isolated from European and African epidemics and are believed to originate from North Africa. Comparative genome analysis revealed that the Cyprus strain contains the N-linked glycosylation site (NYST) in E protein starting at position 154 that is associated with neuroinvasiveness and increased pathogenicity (6).
Discussion: The first evidence of WNV in Cyprus stems from a serological and ectoparasite survey in migratory birds in the Eastern Mediterranean between 1966 and 1971 conducted by the US department of defense. A WNV was isolated from a Barred Warbler, (Sylvia nisoria) was later sequenced and found to belong to lineage 2. Since Cyprus lies on the path of several major migratory bird routes, the introduction of WNV on the island is likely given that several mosquito species of the genus Culex, which are the most important vector of WNV are abundant in Cyprus (7).

In conclusion, we report the complete genome sequence of West Nile virus obtained from the first human case of neuroinvasive WNV infection in Cyprus. Phylogenetic analysis revealed that the virus belongs to lineage 1a.

SA09 IgG from Multiple Sclerosis patients positive for antiphospholipid antibodies increases the activation of p38 MAPK and p65 NF-κB
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Background: Antiphospholipid antibodies (aPL) are known to occur in Multiple Sclerosis (MS) patients, even though their exact role remains unclear. aPL are key in the formation of thrombi in the Antiphospholipid Syndrome (APS) with most studies now focusing on the pro-thrombotic role of antibodies targeting Domain I of β2-Glycoprotein I (anti-DI). In a previous study we have shown the elevated levels of anti-DI and anti-Cardiolipin (anti-CL) antibodies in MS patients compared to Healthy Controls (HC). In the present study, we investigate the possible pro-inflammatory effects of IgG antibodies from MS patients compared to HC in vitro.

Methods: Total IgG was purified from 10 MS patients that were positive for anti-DI and 9 MS patients that were positive for anti-CL antibodies; along with age and gender matched HC groups (negative for both aPL). IgG samples were pooled together in groups according to positivity for either aPL tested for endotoxin. 100 μg/ml of IgG was used to stimulate an astrocytic cell line, U87 at different time points from 10 minutes up to 12 hours. Subsequently, the cells were lysed and cell lysates were quantified and analyzed by immunoblot using antibodies for p38 MAPK and p65 NF-κB.

Results: Phosphorylation of p38 MAPK and p65 NF-κB increased 2-fold with IgG from MS patients compared to HC after 1 hour (for p65 NF-κB, p<0.05). This was also observed using IgG from MS patients positive for IgG anti-DI. Overall, there was a considerable difference in phosphorylation of p65 NF-κB, and a significantly higher phosphorylation of p38 MAPK in astrocytes treated with IgG from MS patients (positive for either aPL) compared to both untreated cells, or cells treated with IgG from HC (p<0.05 for both).

Conclusion: IgG from MS patients positive for aPL, activate inflammatory signaling and may signify a role in pro-thrombotic conditions in MS.
Background and Aim: This presentation will summarize the current state of play in the gene therapy of β-globinopathies, sickle cell anemia and β-thalassemia, with reference to corresponding results of our own research in Cyprus.

Methods: Primary experimental work referred to employs lentiviral gene delivery, RNA interference and TALEN- and CRISPR/Cas9-mediated genome editing in cell lines and primary patient-derived cells.

Results: In preclinical research, substantial success has been achieved in the correction of critical disease parameters by all three principal therapeutic approaches of (i) gene addition of β-globin-like transgenes, (ii) repair of the primary mutation by genome or base editing and (iii) functional correction of β-globin deficiency by re-activation of the primarily fetal γ-globin chain. Gene addition is the longest-established of these approaches and is the only one as yet applied in the clinic, with encouraging results for sufferers of both types of β-globinopathies. Repair of the primary mutation is still hampered by low efficiencies in primary cells but is based on still nascent editing technology with substantial scope for improvement. Finally, the greatest diversity of strategies is dedicated to the activation of fetal hemoglobin, including genome editing, expression of synthetic transcription factors and RNA-interference-mediated knockdown of γ-globin repressors.

Conclusion: Approaches (i) through (iii) have all been vindicated by extant data and, pending optimisation of safety and efficacies, may lead to therapeutic outcomes if applied to patients. Which approach will be preferred in the clinic and who will have access to treatment long-term is hard to gauge at this juncture. Prospects for clinical application and its ubiquity will depend on many additional factors, including cost and market size for corresponding medical products, further technical improvements, changing policies relating to advanced therapies, and modes and patient age of delivery.

Keywords: Anemia, Sickle Cell, beta-Thalassemia, Genetic Therapy, Gene Editing, Fetal Hemoglobin
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Introduction: Colorectal cancer (CRC) ranks among the top cancer types for which immunotherapies are being evaluated. Cytotoxic T cells and natural killer cells can target and kill cancer cells and effector T cells at the tumor site can predict favourable outcome across many cancers. Our aim was to examine the intratumoral immune cytolytic T-cell activity (CYT) of CRC and to investigate how it relates to different aspects of the tumor’s biology.

Materials and Methods: Using TCGA extracted data from 461 cases of colon adenocarcinoma and 172 cases rectum adenocarcinoma we screened the CYT in these two cancer types. The CYT status was compared against the somatic mutational load, microsatellite instability (MSI), copy number alterations, the deregulated expression of KRAS, APC, as well as that of immune checkpoint molecules.

Results: CYT was significantly lower in CRC compared to the normal mucosa. Tumor samples were divided into CYT-low and -high, respectively. The mutation load and CYT in colorectal tumors increased considerably given high microsatellite instability (MSI) vs stable microsatellites (MSS). The mutation load in colon but not rectal tumors increased significantly given the status of cytolytic activity. Most mutations across the datasets were associated with C>T transitions and the frequency of specific substitutions did not differ between CYT-high and CYT-low tumors. The expression of immune checkpoint molecules was also significantly higher in MSI vs MSS CRC. More recurrent somatic copy number alterations were scored in CYT-low vs -high tumors. We further identified the significantly mutated genes occurring in CYT-high and -low CRCs. Multiple inhibitory checkpoint molecules were expressed at markedly higher levels in CYT-high CRCs.

Discussion: Overall, our data show that CYT correlates with higher mutational burden and deregulated expression of several inhibitory checkpoint genes. Combinatorial targeting of these pathways may expand the clinical benefit for CRC patients.
**SA12 Non-invasive prenatal testing of microdeletion syndromes**

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The discovery of cell free fetal DNA (cfDNA) in maternal plasma has greatly facilitated the development of non-invasive prenatal testing (NIPT) of fetal aneuploidies and sub-chromosomal abnormalities, overcoming the risk of spontaneous abortion due to invasive procedures. It has been shown that clinically relevant sub-chromosomal microdeletions and duplications have high prevalence in the general population and have been associated with severe intellectual disabilities and high morbidity and mortality rates. Despite the technological advances in the detection of chromosomal aneuploidies, sub-chromosomal copy number change detection still remains a challenge using current NIPT methodologies. We hereby present a validation study using proprietary target capture enrichment technology for the NIPT of 1p36, DiGeorge, Wolf-Hirschhorn, and Smith-Magenis microdeletion syndromes.

Cell free DNA (cfDNA) was extracted from 785 first trimester pregnancy plasma samples, including one positive sample for Wolf-Hirschhorn syndrome. Additional 54 synthetic samples were created by spiking DNA obtained from affected individuals into cfDNA derived from non-pregnant female samples at concentrations of 5%, 10% and 20%. Enrichment probes were designed to span the critical regions of the four microdeletion syndromes avoiding low copy repeats and repetitive elements. All samples were enriched using target capture enrichment technology followed by Next Generation Sequencing (NGS) as previously described¹. Enriched sequencing libraries were analyzed using a proprietary statistical analysis pipeline specifically designed to test for deletions in each of the syndromes.

The assay was able to correctly classify the abnormal Wolf-Hirschhorn sample and all normal plasma pregnancy samples (n=784) resulting in 100% specificity and sensitivity. Furthermore, all 54 abnormal synthetic samples were correctly classified, with estimated sensitivity 100%.

The clinical impact of cfDNA testing has been significant as indicated by its wide-spread adoption in NIPT. Using proprietary target capture enrichment technology and bioinformatics analysis pipeline we were able to accurately detect all abnormal samples overcoming the limitations of current methodologies. This allows us to expand the number of diseases that can be detected by NIPT by including microdeletion syndromes, thus offering more choices to couples towards an informed management of their pregnancy.

¹Koumbaris et al., Clinical Chemistry 62:6, 848-855, 2016
SA13 Reversal of fetal globin silencing through isoform-specific disruption of the Bcl11a transcription factor

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Background: Sickle-cell disease (SCD) and β-thalassemia are common and potentially life-threatening monogenic disorders. Both are caused by defects in β-globin and are suitable targets for gene-therapy approaches. Pathology for both disorders is significantly alleviated by elevated levels of the fetal β-like globin, γ-globin, whose expression is curtailed in most adults by the BCL11A transcription factor. BCL11A is essential for the survival of lymphoid cells, and its extra-long (XL) isoform is particularly abundant in erythroid cells. To date no isoform-specific functional assessment of BCL11A has been undertaken.

Methods: CRISPR/Cas9 RNA-guided endonucleases (RGENs) were delivered to HUDEP-2 cells using lentiviral (LV) vectors and were utilized to achieve knockout of the γ-globin repressor BCL11A (targeting the start codon and the 5’ region of exon 1, respectively) and of its XL isoform (targeting three isoform-specific zinc finger motifs). Additionally, corresponding dual-promoter LV vectors encoding both the Cas9 endonuclease and sgRNA components were tested in control and patient-derived CD34+ cells.

Results: Highly efficient RGENs for all targets were verified by plasmid transfection and by transduction with LV vectors into the erythroid cell line HUDEP-2, which closely resembles in morphology, gene expression and differentiation behaviour adult CD34+ cells. Immunoblots demonstrate that expression from integrating LVs in Cas9-transgenic HUDEP-2 cells resulted in depletion of the targeted BCL11A isoforms, strong derepression of γ-globin and, for isoform-specific RGENs, in stable truncated BCL11A proteins. The same cells also showed a slight delay in erythroid differentiation compared to control-treated samples for all BCL11A target sites, indicating a positive role of BCL11A and BCL11A-XL in erythroid differentiation in general and thus conceivable side-effects of the chosen approach in the erythroid lineage upon possible clinical application. After functional proof of the efficiency of dual-promoter LVs in HUDEP-2 cells, they were validated in primary CD34+ cells from β-thalassaemia patients. All performed analyses confirmed robust and highly significant γ-globin reactivation in human CD34+ cells, without disturbing erythropoiesis.

Conclusions: Our study investigated the structure-function relationship for the BCL11A transcription factor and its isoforms. BCL11A-XL deactivation allows γ-globin induction and thus possible therapeutic exploitation, whereas potential detrimental effects, in particular in the lymphoid lineage, remain to be investigated.
SA14 A novel localization and function of acid ceramidase, a key regulatory enzyme of ceramide metabolism

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Acid ceramidase (AC) is key regulatory enzyme that is implicated in the metabolism of ceramide (Cer). AC is present in the lysosomes where it is responsible for the degradation of Cer into sphingosine and free fatty acids. A substantial body of evidence has accumulated from recent studies which shows that AC may have different localizations, and consequently different functions, other than lysosomal degradation of ceramide. Importantly, AC also has ‘reverse’ enzymatic activity, which results in the synthesis of Cer, the main precursor for higher order glycosphingolipids. However the physiological significance as well as the specific subcellular localization for the reverse activity remains unknown. The involvement of AC in the pathogenesis of various diseases (e.g. Farber Disease, Spinal Muscular Atrophy, cancer and diabetes) and its correlation with a broad range of molecular processes (e.g. apoptosis, signal transduction and autophagy) underlines its critical role and its biological significance in the cell.

The present work is focused on the subcellular localization and function of AC in different epithelial and neuronal cell lines. We show that AC, apart from its lysosomal distribution, is strongly localized at the Golgi complex (GC) and endoplasmic reticulum. Furthermore, we demonstrate that AC is an integral membrane protein that co-segregates with the GC after the depolymerization of microtubules. In addition, we show that depletion of AC in epithelial cells alters the morphological profile of many resident proteins of the GC, suggesting a possible role of this enzyme in the structure and/or function of this organelle. The morphology of the GC is also affected after expression of the Thr42Met mutation, causing Spinal Muscular Atrophy with Progressive Myoclonic Epilepsy, compared with the untransfected cells or cells expressing the Tyr36Cys mutant causing Farber disease. We also illustrate the dynamic behavior and the subcellular trafficking of AC in a live SHSY-5Y cell line, showing that it is localized in vesicles with both retrograde and adenograde axonal movement. Disruption of microtubules in these cells results in the formation of larger vesicles with reduced mobility.

Our study provides novel data regarding the localization and function of AC in mammalian cells, beyond its function in the degradation of Cer inside the lysosomes. We expect that our results will shed new light onto the physiological role of AC in normal and pathological conditions, thereby facilitating potential therapeutic intervention.
PA01  Investigation of genetic and environmental determinants of Parkinson’s disease in the Cypriot population  

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Parkinson’s disease (PD) is a neurodegenerative disorder with complex pathogenesis implicating both genetic and environmental risk factors. The majority of studies for the identification of genetic and environmental determinants of PD were conducted in Northern Europe and North America. This is the first epidemiological case-control study investigating risk factors for PD in the Cypriot population.  

A cohort of 235 PD patients and 464 healthy age matched controls were recruited. Demographic and lifestyle data was collected. Sixteen previously reported SNPs associated with PD were genotyped. Regression analysis examined the association between a number of environmental and genetic factors and PD. Interaction analysis explored potential gene-environment interactions among Cypriot PD cases and controls. Multivariate logistic regression demonstrated fish consumption, and heavy smoking to be inversely associated with PD risk. Conversely, red meat and nuts consumption, severe head injury and exposure to both pesticides and other chemical substances were positively associated with the onset of PD. There was a significant association detected between rs4998386 and PD only among light coffee drinkers. Interaction analysis for gender and genetic variants revealed 4 SNPs (rs7617877, rs823118, rs356182, rs2896905) significantly interacting with gender to influence PD status. Moreover rs2896905 SNP, which is located in the SLC2A13 gene, was significantly interacting with coffee consumption in this PD case control sample.  

Gender and coffee consumption were shown to affect the association between certain SNPs and PD. The results of the present study concerning epidemiology of PD in the Cypriot population were consistent with other larger studies conducted in other European populations. However, due to sample size constrictions possibly some determining factors for PD were missed.

PA02  Development of a maternal carrier screening test from cfDNA using target capture enrichment and a novel bioinformatics pipeline  

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Identification of a fetus’ predisposition to autosomal recessive conditions that can be
inherited from the parents is considered an important part of prenatal care. Once a risk factor for such a condition is identified, the couple can then make informed reproductive decisions during pregnancy. Towards this goal we designed a novel approach where the carrier status of the mother can be determined for a given set of heritable genetic abnormalities, from the maternal plasma sample collected for non-invasive prenatal testing.

Cell free DNA (cfDNA) was obtained from 706 first trimester pregnancy plasma samples referred for the VERACITY test and an enriched sequencing library was prepared using custom TArgeted Capture Sequences (TACS) as previously described. TACS were specifically designed based on genomic locations of known mutations involved in heritable genetic conditions in order to determine the carrier status of the mother. In total, fourteen different genes, covering a total of 157 loci were interrogated. The enriched products were sequenced using Next Generation Sequencing (NGS) and subsequent data was processed using a custom bioinformatics pipeline which provides results on the status of maternal genetic conditions. For all 706 samples the VERACITY result was successfully reported. Overall 12 unique pathogenic mutations were identified for beta thalassemia, cystic fibrosis, phenylketonuria, autosomal recessive polycystic kidney disease and Gaucher’s disease from a total 61 carrier mothers. A subset of mutations was independently confirmed by Sanger sequencing using DNA obtained from maternal buffy coat and oligonucleotides designed against the regions of interest.

This novel approach allows for the determination of maternal carrier status from cfDNA referred for NIPT. It is cost effective as both NIPT for common aneuploidies and carrier screening are simultaneously performed using proprietary TACS enrichment technology. Paternal carrier status can subsequently be determined for genetic conditions where the mother is found to be a carrier. With this approach we can provide rapid prenatal carrier screening results for both partners. Most importantly, the risk factor of the fetus for the genetic conditions for which the parents are carriers can be determined, allowing the couple to take informed decisions during pregnancy.


PA03 Development of non-invasive method for assessing circulating tumour DNA in patients with solid tumours.

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It is estimated that more than 14 million people are diagnosed with cancer each year. Current practice relies on molecular and histopathology results derived from invasive tissue biopsy, which has several drawbacks. Circulating tumour DNA (ctDNA) found in plasma may provide a non-invasive means for early cancer detection, diagnosis and
monitoring not otherwise possible with conventional testing. We developed an assay based on a proprietary technology for the detection of cancer mutations in a patient’s plasma and tissue. Reference material was used for the proof of concept study which exhibited a limit of detection (LOD) between 0.1-1% minor allele frequency (MAF).

A total of 453 driver and clinically actionable mutations across 48 genes were targeted. We used plasma and matched tissue samples from cancer patients for clinical pre-validation. Driver cancer mutations were detected between patient-matched tissue and plasma. We detected hotspot mutations in PI3KCA with MAF ranging from 32-63% in tissue and 1.4-6% in plasma from non-metastatic breast cancer in a number of patients. TP53 hotspot mutation was also identified with MAF at 60.6% and 4.9% in tissue and plasma respectively.

PA04 Baseline Regenerative Signalling Drives Tumorigenesis in Drosophila

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Despite the established link between the inflammatory microenvironment and tumor initiation and progression, the causal players of this interaction are unclear. Germline mutations account for the 10% of colorectal cancer (CRC) incidence, whereas the vast majority of cancer promoting factors associates with somatic mutations and environmental elements, including chronic inflammation and bacterial infections. For instance, the chronic inflammation of the gastrointestinal mucosa in Inflammatory Bowel Disease (IBD) patients is a key predisposing factor for developing CRC. Nevertheless, so far only Helicobacter pylori bacterial infection has been established as a causative agent of gastrointestinal inflammation and cancer. In mammals areas with active inflammatory responses accompanied by a high rate of epithelial cell-turnover and sustained DNA damage are sufficient to drive carcinogenesis. Still the genes and processes that initiate tumorigenesis and link inflammation to cancer remain obscure.

Herein, we used Drosophila to model human pathogen-elicited intestinal infection and tumorigenesis, providing a causative link between intestinal damage and mutant stem cell-derived tumors. Homeostasis in the intestinal epithelium of Drosophila is retained by intestinal stem cells (ISCs) that amplify through mitotic divisions giving rise to SCs and transient enteroblasts, which normally differentiate without further divisions into either absorptive enterocytes or enteroendocrine cells. Our quantitative population genetics study, including the screening of 153 wild type strains of the Drosophila Genetic Reference Panel (DGRP), demonstrates that epithelial intestinal mitosis and inflammatory signaling drive regeneration and predispose for tumorigenesis. Drosophila strains exhibiting excessive mitosis upon infection can be predicted based on the higher baseline mitotic activity and the increased baseline expression of DI/DLL1, upd3/IL-6, vein/EGF and eiger/TNF, the ligands of the Notch, JAK/STAT, EGFR and TNFR pathways,
respectively. These pathways are highly conserved in mammals and their role in mammalian epithelial regeneration has been elucidated, but their role in cancer has not been studied. Accordingly, we find that highly mitotic strains colonized with pathogenic bacteria are more prone to tumor development caused by chemical inhibition of the tumor suppressor gene, Notch or upon aging. Moreover, we show that epithelial cells undergo endoreplication to compensate for cell loss when mitotic activity is limited. These results provide a framework for the study of various predisposition factors that are linked to intestinal stem cell mitosis at the initial stages of intestinal tumorigenesis.

**Keywords:** regenerative inflammation, genetic background, intestinal microbes, stem cell mitosis, tumorigenesis

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**PA05**  Characterization of a novel σ1R mutation in Jerash type dHMN

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Distal hereditary motor neuronopathies (dHMNs) comprise a genetically and clinically heterogeneous group of motor neuron diseases. dHMN Jerash hereditary motor neuronopathy, found in the Jerash region of Jordan, is characterized by weakness and atrophy of the lower limbs at the ages between 6 and 10 years old. These symptoms spread to the upper limbs in no more than 2 years, and progress with the passage of time. We have identified a novel missense mutation in the σ1R gene in patients with Jerash type dHMN and initiated functional analysis in order to confirm/exclude this variation as the disease-causative mutation. σ1R (sigma-1 receptor) is a chaperone protein localized at the interface between endoplasmic reticulum (ER) and mitochondria, that is widely expressed in various human tissues and enriched in motor neurons. It is also implicated in many cellular activities, such as ion channel modulation, lipid transport, ER stress response, autophagy, synaptogenesis, and agonists of σ1R possess neuroprotective properties. σ1R has been studied in various diseases like amnesia, schizophrenia, Alzheimer disease, juvenile amyotrophic lateral sclerosis and depression.

σ1R mutations have already been implicated in dHMNs since they have been associated with a case of dHMN in a consanguineous Chinese family, and two dHMN cases in distinct Italian families. Also, the loss of σ1R's function mediates motor neuron degeneration.

To perform the functional studies, lymphoblastoid cell lines were established from Jerash dHMN patients and healthy individuals’ blood. Also, plasmid constructs expressing heterologous σ1R-wild type and σ1R-mutated proteins were generated. So far, mRNA and protein expression, as well as subcellular localization studies have been completed. Our results indicate that even though mRNA levels of the two forms of σ1R (mutant and WT) are quantitatively similar, the endogenous protein levels of the mutated σ1R from patients’ lymphoblastoid cells are demolished in comparison to the control samples. Moreover, a significant drop in protein levels was observed in the case of the heterologous mutated Flag-σ1R in comparison to the wild-type Flag-σ1R, both in human and mouse cell lines. In the presence of the proteasomal inhibitor MG132, mutated Flag-σ1R protein
levels were elevated, demonstrating that the mutant σ1R is degraded through the ERAD (Endoplasmic-Reticulum-Associated protein Degradation) pathway. Immunofluorescence experiments showed that although both wild-type and mutated σ1R are localized at the endoplasmic reticulum, the mutant form exhibits a more diffused distribution and a lower expression level. This data demonstrate that this specific missense mutation is the Jerash dHMN disease-causing mutation, by altering physiological σ1R’s expression and localization. Further experiments are currently taking place to unravel the effect of the mutation in ER stress response, autophagy and apoptosis.

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PA06 Genetic predisposition to Triple negative breast cancer in Cyprus

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Breast cancer (BC) is the most common cancer in women and the second leading cause of cancer-related mortality. Triple Negative breast cancer (TNBC) is a distinct aggressive form of BC characterized by lack of expression of the estrogen and progesterone receptors (ER/PR) and the human epidermal growth factor receptor 2 (HER2) in tumour material. It accounts for approximately 12-15% of all breast cancer cases and it occurs most frequently in young or premenopausal women. Triple negative tumors are often aggressive and more difficult to treat with the five-year survival rate estimated at 70% compared with >80% for all other subtypes. Recently it has been reported that around 15% of all TNBC patients have deleterious mutations in predisposition genes. Of these 11% had mutations in the BRCA1 gene, 3% in the BRCA2 gene and the rest in other genes mostly involved in homologous recombination including PALB2 and RAD51C. The aim of this study was to assess the frequency and distribution of mutations in Cypriot TNBC patients unselected for family history of breast and ovarian cancer who were tested negative for germline mutations in the BRCA1 and BRCA2 genes and determine the utility of performing panel testing for this group of patients. This pilot study involved 42 TNBC patients. Genomic DNA was sequenced using the Illumina Trusight Cancer sequencing panel which targets 94 genes and 284 SNPs associated with a predisposition towards various cancers. Initial analysis was restricted to the 13 known breast cancer predisposition genes namely BRCA1, BRCA2, PALB2, BRIP1, RAD51C, RAD51D, NBN, ATM, CHEK2, TP53, PTEN, STK11, and CDH1. Further analysis involving the other 81 genes included in the panel will be
performed at a second stage. Three deleterious mutations, two in the PALB2 gene and another one in the TP53 gene were detected in 3 unrelated TNBC patients. Furthermore, 6 variants of unknown clinical significance (VUS) were identified in the BRIP1, ATM, TP53, STK11 and PALB2 genes. It is noted that the STK11 VUS has not been reported before. Our results suggest that deleterious mutations in breast cancer predisposition genes other than BRCA1/2 are present at a relatively high frequency in Cypriot patients with TNBC unselected for family history of cancer. Further studies using a larger cohort of TNBC patients are needed in order to confirm these results and conclude whether panel testing should be offered to this group of patients irrespective of their family history.

PA07  Twin to Twin Transfusion Syndrome: A Meticulous Study
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Introduction: Twin to twin transfusion syndrome (TTTS) is a rare progressive disease of the placenta, occurring due to a compilation of disproportionate blood supply, by which one baby (recipient) receives more blood than the other (donor), occurring in monochorionic pregnancies.

Background: Since the twins are sharing a simple placenta, their blood supplies can become connected, which sometimes leads to unbalanced blood transfer between the twins. The occurrence of the syndrome depends on the number, type and direction of the interconnecting blood vessels (anastomoses), because they are responsible for this “flow imbalance”. The donor twin’s most common defects are reduced blood volume, defective organs and systems development, and decreased urinary output, leading to very low levels of amniotic fluid and inducing “oligohydramnios”. The recipient twin’s is “overloaded” with blood and a “polyhydramnios”, usually leading to heart failure.

Materials and Methods: A systematic review was performed into the International Literature using databases as: MEDLINE, Pub Med and WHO. The review was restricted to articles published from 2000-2017. Staging of TTTS was also reviewed as performed by Quintero on 1998, as well as new information trends about TTTS Staging.

Results: TTTS occurs about 15% of the time among identical twins and has a mortality rate of 60 to 100%, if left untreated. It is not a hereditary condition and latest data state that it cannot be prevented. Pregnant mothers having symptoms must urgently visit their gynecologists. Technological development and scientific knowledge, however, have proposed new fundamental treatment options for this condition. Some of the most common are Fetoscopic Laser Surgery, Amniocentesis and Three-Dimensional Virtual Placentoscopy, while earlier Umbilical Cord Occlusion or even delivery of the twins would be proposed.

Conclusion: TTTS is a random event and latest scientific methods can be used just for its treatment, not its prevention. Various studies have suggested the advantages of
Fetoscopic Laser over other treatment choices and it has been the primary one of the last decade.

References:

PA08  REVERSAL OF FETAL GLOBIN SILENCING THROUGH ISOFORM-SPECIFIC DISRUPTION OF THE BCL11A TRANSCRIPTION FACTOR

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Background: Sickle-cell disease (SCD) and β-thalassemia are common and potentially life-threatening monogenic disorders. Both are caused by defects in β-globin and are suitable targets for gene-therapy approaches. Pathology for both disorders is significantly alleviated by elevated levels of the fetal β-like globin, γ-globin, whose expression is curtailed in most adults by the BCL11A transcription factor. BCL11A is essential for the survival of lymphoid cells, and its extra-long (XL) isoform is particularly abundant in erythroid cells. To date no isoform-specific functional assessment of BCL11A has been undertaken.

Methods: CRISPR/Cas9 RNA-guided endonucleases (RGENs) were delivered to HUDEP-2 cells using lentiviral (LV) vectors and were utilized to achieve knockout of the γ-globin repressor BCL11A (targeting the start codon and the 5' region of exon 1, respectively) and of its XL isoform (targeting three isoform-specific zinc finger motifs). Additionally, corresponding dual-promoter LV vectors encoding both the Cas9 endonuclease and sgRNA components were tested in control and patient-derived CD34+ cells.

Results: Highly efficient RGENs for all targets were verified by plasmid transfection and by transduction with LV vectors into the erythroid cell line HUDEP-2, which closely resembles in morphology, gene expression and differentiation behaviour adult CD34+ cells. Immunoblots demonstrate that expression from integrating LVs in Cas9-transgenic HUDEP-2 cells resulted in depletion of the targeted BCL11A isoforms, strong derepression of γ-globin and, for isoform-specific RGENs, in stable truncated BCL11A proteins. The same
cells also showed a slight delay in erythroid differentiation compared to control-treated samples for all BCL11A target sites, indicating a positive role of BCL11A and BCL11A-XL in erythroid differentiation in general and thus conceivable side-effects of the chosen approach in the erythroid lineage upon possible clinical application. After functional proof of the efficiency of dual-promoter LVs in HUDEP-2 cells, they were validated in primary CD34+ cells from β-thalassaemia patients. All performed analyses confirmed robust and highly significant γ-globin reactivation in human CD34+ cells, without disturbing erythropoiesis.

**Conclusions**

Our study investigated the structure-function relationship for the BCL11A transcription factor and its isoforms. BCL11A-XL deactivation allows γ-globin induction and thus possible therapeutic exploitation, whereas potential detrimental effects, in particular in the lymphoid lineage, remain to be investigated.

**PA09** SIMILAR MOTOR RESPONSES DURING CONTRACTION AND RELAXATION WHILE STIMULATING THE MOTOR PATHWAY OF THE CENTRAL NERVOUS SYSTEM.

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**Objective:** Transcranial Magnetic Stimulation (TMS) of head and spinal cord is a non-invasive method that assesses the integrity of the central motor pathway using a stimulating coil resulting in a motor response, the Motor Evoked Potential (MEP), recorded from a peripheral limb muscle. A phase is part of the motor unit response that falls between two baseline crossings. Previous studies suggest that voluntary muscle contraction increases the appearance of MEP polyphasia in patients with genetic generalised epilepsy, amyotrophic lateral sclerosis and other conditions. In this study, we examined 30 healthy individuals with the use of TMS, in order to evaluate the probability of polyphasia appearance during both muscle contraction and relaxation.

**Methods:** Normal volunteers were studied with the use of MEP in two different stages; contracted and relaxed. Both stages were examined with the use of a circular coil and the contracted stage was also examined with a butterfly shaped coil as it was reported to give more focused stimulation. The muscles examined were the abductor digiti minimi in the hand and the tibialis anterior in the lower limb.

**Results:** Only four individuals were found to have polyphasia during the contracted state in the upper limbs using the butterfly coil and two additional individuals using the circular coil during contraction of the tibialis anterior, which is only 20% of all individuals examined.

**Conclusion:** Voluntary muscle contraction of targeted muscles does not always trigger the appearance of polyphasia in motor responses.

**Significance:** Our findings suggest that contraction and relaxation of targeted muscles give similar motor responses and that voluntary muscle contraction does not increase the appearance of MEP polyphasia compared with relaxation in the majority of cases.
This has relevance for future studies where the appearance of polyphasic waveforms, and thereby alterations in central neurophysiology, like in Epilepsy will be the main focus of the research.

**Keywords**: Motor Responses, Polyphasia.

PA10  Risk factors of arterial ischemic stroke in Polish children in dependence on stroke subtype

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**Background**: The aetiology as well as risk factors of childhood arterial ischemic stroke (AIS) are still not fully known. However, multiple risk factors may have impact on its outcome. The aim of this study was to analyse risk factors of arterial ischemic stroke in Polish pediatric patients depending on stroke subtype.

**Material and Methods**: A group of 77 children (mean age 8.3±5.4 years), white, Polish Caucasians, with their first AIS were retrospectively analysed in the study. Patients were recruited in the Department of Pediatric Neurology at the Medical University of Silesia in Katowice (Poland). Statistical analysis was performed using STATISTICA 12.0.

**Results**: The most frequent stroke subtype in the studied group was TACI (present in 32% cases). Sex significantly differentiated the stroke subtypes (p=0.030). Boys were more prevalent among children with POCI (90%) and TACI (68%) subtypes. At the time of AIS appearance 44% of children were sleeping. Similar percentage of cases (38%) were scored with 10 Apgar points after birth and almost all patients were born at time of full-term pregnancy. The age at onset, Apgar points, birth weight, foetal age, complication of pregnancy as well as the position of the body’s patients at the time of AIS did not significantly differ between stroke subtypes. We observed significant differences between subtypes of AIS and seasons of the year at which the AIS occurred (TACI subtype appeared most frequently in the summer, LACI – during winter or spring and PACI – in the winter or autumn). There were also associations between focal cerebral arteriopathy (FCA) as well as chronic diseases and types of AIS. Both of the factors were the most frequent in children with TACI and PACI (FCA - 80% and 79%, respectively; chronic diseases - 36% and 43%, respectively).

**Conclusions**: FCA, one of the most characteristic risk factors of pediatric AIS, predisposes to stroke of TACI and PACI type.

**Key words**: Arterial ischemic stroke, risk factors, focal cerebral arteriopathy, children
Overexpression of a novel missense MFN2 mutation leads to mitochondrial dysfunction

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Introduction: Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy of the peripheral nervous system (1/2500 individuals). We identified a novel missense MFN2 mutation in a multigeneration Cypriot CMT2A family. The MFN2 gene product is localized on the outer mitochondrial membrane and plays a significant role in the fusion of mitochondria. This study is focused on the functional analysis of the identified MFN2 point mutation.

Materials and Methods: Total RNA was extracted from available patient and control lymphoblastoid cell lines and the whole cDNA was synthesized. The whole coding cDNA of MFN2 gene from patient (mutant) and control (wild-type) was amplified and inserted into a cloning vector. Transfections of the mutant and the wild-type plasmids into neuronal cells were performed and extracted protein and mRNA levels were evaluated. Transfected cells with both plasmids were fixed and incubated with fluorescent antibodies targeting the MFN2 protein and. Axonal transport was assessed on transfected cells, investigating the expression of the proteins (Kinesin, Dynein, Tubulin and Tau) by Western blotting. Finally, time-lapse confocal microscopy was used in order to study mitochondrial dynamics.

Results: Similar expression between the mutant and the wild-type gene was observed at the protein and mRNA levels. Both normal and mutant allele had the same localization into cells. Western blot analysis indicates that, there is no difference at the expression level of motor (Kinesin, Dynein) and Tau proteins between the mutant and wild-type transfected cells. An increase of Tubulin levels was observed in the mutant MFN2 lysate. Furthermore, time-lapse confocal microscopy revealed that when Mfn2-Myc is expressed in Mfn1/Mfn2-null mouse embryonic fibroblasts, it causes very severe mitochondrial aggregation, with all the mitochondria clustered into a perinuclear mass. In contrast, when wild-type Mfn2-Myc gene is expressed in these cells, it rescues the Mitofusin defect and promotes mitochondrial elongation.

Conclusion: Despite mutations in MFN2 being the most commonly identified cause of axonal CMT, the mechanism which leads to the axonal degeneration is not yet clear. Funded by the Cyprus Research Promotion Foundation (Grant #: 0311/23).
PA12 Annonasin from Graviola Extract Promotes Selective Cancer cell death In vitro and In vivo via NKA and SERCA Downregulation Pathway
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Abstract: Phyto-compounds are beneficial in healthcare sector, there contribution in Medicine is well recognized. Studies have demonstrated the progressive effects of phyto-compounds on immune related diseases and to the cancer patients’ quality of life improvement. Graviola is an evergreen tree where its extracts (leafs, seeds) are known to be beneficial against cancer. Graviola reported to have anti-tumor properties by promoting cancer cell death. Here, we are demonstrating the positive effect of Graviola in different cancer cell lines such as HeLa, Pancreatic, Prostate, Breast and laryngocarcinoma. Our results reveal a strong promotion of cell death in dose of 1mg/ml in vitro and 25mg/kg in vivo. The key finding of the present study is that Graviola promotes cell death via downregulation of Na+/K+-ATPase and SERCA pumps respectively. Moreover, the effects on normal cells also examined in vitro and in vivo, showing limited/no-toxic effects on normal cells. Overall our results suggest that this compound could be a strong agent against cancer.

PA13 Comparative proteomic analysis of mouse kidney with systemic lupus erythematosus
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Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder with diverse clinical presentations. It is considered one of the most heterogeneous autoimmune diseases characterized by the presence of pathogenic autoantibodies, chronic immune dysregulation and inflammation that may lead to life-threatening end-organ damage.
Renal involvement in SLE, known as lupus nephritis (LN), affects about two-thirds of patients during their life-time and it is among the most severe and frequent complications of SLE associated with poor long-term prognosis. Currently, routine methods of assessing renal damage and activity in SLE are of limited sensitivity and specificity. Using mass spectrometry (MS)-based proteomic approaches, we examined alterations in the protein expression profiles of kidneys between a B6.NZMsle1/sle2/sle3 lupus mice model and the respective control mice, at different disease stages, in order to gain molecular insights into disease pathogenesis and identify potential LN biomarkers that may be useful for prediction and disease progression improving therapeutic management.

**Methods**: Kidneys were harvested from female triple congenic B6.NZMsle1/sle2/sle3 lupus mice model and sex and age-matched C57BL/6 control mice at three different time points, 12-, 24- and 36-weeks, representing different stages of LN. Proteins were extracted from kidneys, purified, reduced, alkylated and digested by trypsin in a three day procedure. Purified peptides were separated by liquid chromatography (1D-LC) and analyzed by electrospray ionization quadrupole time-of-flight MS (ESI-QTOF-MS). Particularly, a label-free MS approach was performed using the UDMS E strategy, a data-independent acquisition (DIA) MS method that uses ion mobility drift time-specific collision energy profiles. Data were processed by the Progenesis QIp and functional annotation analysis performed using multiple bioinformatics resources.

**Results**: About 3000 non-redundant proteins were identified in all samples. Several hundred proteins including immunoglobulins, histones and glycoproteins were identified to be altered, resulted from the comparison of proteomic profiles of disease and control mice kidneys. In total, 629 proteins including immunoglobulins and histones were found to be significantly dysregulated with a p-value <0.05 and a fold change >1.5 OR <0.67 at all three time points. Further pathway analyses showed that the identified dysregulated proteins were involved in multiple pathways including, mitochondrial electron transport chain, cell redox homeostasis, actin-binding and immune system, which are known to be associated with autoimmune diseases.

**Conclusions**: Using MS-based proteomic analyses of mice kidneys with SLE at different stages, we identified a number of proteins that are implicated in LN development and hence, they can serve as potential biomarkers of LN. Interestingly, some proteins showed dysregulation already at 3 months of age prior to clinical symptoms. These proteins could serve as potential early prognostic as well as diagnostic markers of LN, providing new insights about molecular mechanisms implicated in LN pathogenesis. It is important to diagnose disease activity in the kidney as early as possible, given the fact that early intervention is associated with better disease outcome in LN. In addition, proteins that were observed to be altered along with LN are of great value, as they can be used as potential disease activity biomarkers. Further work is underway in order to validate and confirm these results with other methods such as Multiple Reaction Monitoring (MRM).
western blot and Immunofluorescence/Immunohistochemistry, as well as in human clinical samples.

**PA14  Contribution of NGS towards the molecular diagnosis of cerebellar ataxias and spastic paraplegias in the Cypriot population**

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Cerebellar ataxias (CA) and hereditary spastic paraplegias (HSP) are two groups of neurodegenerative diseases characterized by vast genetic and phenotypic heterogeneity. A partial clinical overlap is also often observed between them, resulting in more complex phenotypes termed as spastic ataxia (SA). Therefore, molecular genetic diagnosis becomes challenging and many families and sporadic patients remain undiagnosed despite extensive testing. However, the recent advent of next-generation sequencing (NGS) has enabled the efficient diagnosis of many patients and the discovery of new genes. Following our recent identification of a novel homozygous GBA2 gene missense mutation by the combined use of whole-genome homozygosity mapping and whole exome sequencing (WES) in an SA family, additional families and sporadic patients have been investigated using NGS. We hereby present our findings enabling the successful diagnosis of two additional autosomal recessive ataxia and three SA families, as well as of three sporadic SA patients of Cypriot origin.

WES of the proband from each family and one sporadic patient were performed, whereas targeted gene panel NGS was performed for the second sporadic patient. Both approaches included bioinformatics analysis and were followed by Sanger sequencing validation and segregation studies of the candidate variants. Screening in normal control Cypriot chromosomes was also performed in order to conclude on the causative mutations. For the analysis of the third sporadic patient, Sanger sequencing at the RNA level of a single gene was applied.

This investigation resulted in the identification of eight different mutations in six genes. Overall, a novel homozygous missense mutation in the SPG7 gene, a homozygous frameshift mutation (two base pair deletion) in the SPG11 gene, a novel homozygous nonsense mutation in the ANO10 gene, a homozygous missense mutation in the CLN6 gene and two compound heterozygous missense mutations (a novel and a known) in the FA2H gene, were identified in the five families. The same two FA2H mutations, a novel homozygous frameshift mutation (single base duplication) in the CYP7B1 gene and the above SPG11 mutation in compound heterozygosity with another frameshift mutation (single base insertion), were identified in the three sporadic patients respectively. Genotype-phenotype correlation, considering the prominent symptoms of other patients reported to have mutations in the corresponding genes, enabled confirmation of the genetic findings.

In conclusion, NGS analysis enabled rapid diagnosis of five additional Cypriot families.
and three sporadic patients which have been studied for many years. This study expands the spectrum of the CA and HSP mutations in the Cypriot population. Moreover, the robustness of WES towards the efficient molecular diagnosis of patients and the identification of novel mutations in rare diseases is further supported.

PA15 ESSENTIAL THROMBOCYTHEMIA, A MIDDLE AGED DISEASE AFFECTING A 4 YEAR-OLD CHILD. REPORT OF A VERY RARE CASE WITH DIAGNOSTIC SUBSTANTIATION.

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Essential thrombocythaemia (ET) is a chronic, clonal disease, included within the family of myeloproliferative neoplasms. ET is usually considered to be a disease of the middle-aged, but with the advent of automated platelet counting, it is diagnosed with increasing frequency in young adults and, even more rarely, in children. The actual annual incidence of ET in patients between the ages 0 and 14 years, is currently estimated to be 0.09 per million.

Since the diagnosis of ET is decided upon by exclusion, hereditary thrombocytosis must be ruled out, especially in paediatric cases, with assessment based on the grounds of bone marrow histological examination, in accordance with the genetic profile of the patients.

Herein we present a rare case of a 4-year old female patient with ET. Flow cytometry analysis for peripheral blood and bone marrow did not reveal increased lymphoid or myeloid progenitors, but abnormal myeloid patterns of maturation were observed. Bone marrow biopsy by histopathology revealed a marked megakaryocytic line proliferation, presenting with multiple shape and size megakaryocytes, mostly of large size, with multilobulated and multiform nuclei, often found in small, loose aggregates. Megakaryocytes exhibited no substantial disorder in their nuclear-cytoplasmic ratio, raising the necessity of the JAK2 V617F mutation (Janus kinase 2 gene) evaluation, even though it is not usually found in children. Molecular testing of the bone marrow aspirate revealed the presence of the JAK2 V617F mutation, confirming the ET diagnosis as a hallmark mutation.

This rare case highlights the importance of molecular investigation in confirming the diagnosis of ET and the necessity of multi-centre collective collaboration, for such cases.

PA16 FAMILIAL INCIDENCE OF NON HODGKIN’S LYMPHOMA IN TWO SISTERS. EVIDENCE OF UNKNOWN GENETICAL BACKGROUND, IN THE EVOLUTION OF THE DISEASE.

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Non Hodgkin lymphomas (NHL) of B-cell origin, are a group of haematological malignancies, not known to have any hereditary background. Although all lymphomas in this group share some common genetic defects, resulting in the restriction of immunoglobulin light chains and loss of surface membrane immunoglobulin by B cells in extramedullary sites, no genetic predisposition has been reported yet, in patients of the same family.

Furthermore, it is well known that in patients with follicular lymphomas, t(14;18)(q32;q21) occurs in 90% of cases, causing the overexpression of BCL2, a protein of the mitochondrial membrane, which prevents cells in follicular centres from undergoing apoptosis. The disease may transform to diffuse large B cell lymphoma in 20 - 30% of the cases, rarely to Burkitt / Burkitt-like lymphoma or B cell acute lymphoblastic lymphoma/leukemia.

We present the cases of two sisters aged 72 and 64 years old, who were diagnosed with follicular and diffuse B-cell lymphoma accordingly, both in the grounds of histology and immunohistochemistry, as well as with molecular pathology techniques.

Although the exact gene changes involved in the different types of NHL have been well characterized it is possible that other genes may also need to be elucidated that may have a role with a close family that may be associated with NHL as indicated in the present study.

PA17 WHICH ENVIRONMENTAL FACTOR IS CORRELATED WITH LONG-TERM MS INCIDENCE TRENDS: RECEIVED ULTRA-VIOLET B RADIATION OR GEOMAGNETIC DISTURBANCES?

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Background: The actual nature of the environmental risk factor(s) of multiple sclerosis (MS) is still subject of debate. Received ultra-violet (UV) B radiation and geomagnetic disturbances (GMD) both are solar-terrestrial phenomenon. Insufficient received UV is regarded the main environmental risk factor (RF) for MS in the vitamin D deficiency hypothesis (VDH). Nevertheless, GMD has also been proposed as a potential trigger for MS in the GMD hypothesis.

Objectives: The aim of this study was to investigate which of these mentioned RF is correlated with long-term MS incidence alterations in the high latitude European sites.

Methods: For conducting this study we needed three sets of data including: long-term MS incidence data, long-term GMD data and long-term local received UV data. The PubMed was searched to find studies with reported “annual incidence of MS” for at least 20 consecutive years, from high latitude European countries. Accordingly, six published reports including long-term incidence reports of the United Kingdom 1990-
2010, Denmark 1950-89, Tayside county (Scotland) 1970-1999, Nordland County (Norway) 1970-2009, the Orkney islands (Scotland) 1941-1982 and the Shetland Islands (Scotland) 1938-85 were selected for this retrospective time-series study. Ap index data, as the main GMD index, were extracted from Goddard space flight center and geomagnetic indices database of National Geophysical Data Center. Two sources were used for obtaining long-term local received UV data: the PROMOTE UV record and the COST 726 project. Possible lead-lag relationships between mentioned variables were evaluated by cross-correlation analysis for lags between 0 and 5 years.

**Results:** Significant positive correlations between GMD and MS incidence were seen in Tayside County (at lag of 2 years: $r_s = 0.38$), Denmark (peak correlation at lag of 2 years: $r_s = 0.53$), and UK (at lag of 1 year: $r_s = 0.50$). We found a positive correlation between received UV and MS incidences in the Nordland at lag of 1 year ($r_s = 0.49$).

**Conclusion:** This study found significant positive correlations between alterations in GMD with alterations in long-term MS incidence in three out of six studied locations and supports the GMD hypothesis. The observed significant correlation between MS and UV is positive; hence it is not supportive for UV related vitamin D deficiency hypothesis. Based on the result, GMD hypothesis deserves to be considered by MS researchers in the future studies.

**PA18 Cross-reactivity of antibodies with Neural Precursor Cells in Experimental Autoimmune Encephalomyelitis**

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**Background:** Experimental Autoimmune Encephalomyelitis (EAE), animal model of Multiple Sclerosis, combines T- and B-cell production. Autoantibodies are able to reach the Central Nervous System through the disrupted blood brain barrier and target various cells.

**Goals:** We examined the cross reactivity and identification of the EAE autoantibodies in naive mouse brain of three developmental stages.

**Methods:** EAE was induced in C57BL/6 mice immunized with MOG35-55. On day 17 (Acute Phase) blood-sampling was performed in EAE and NAIVE groups and corresponding antisera (EAE-AS, NAIVE-AS) were collected. The antisera were tested for the presence of autoantibodies by Western Blotting on normal spinal cord and Neural Precursor Cells (NPCs) lysates. Double and triple immunofluorescence (dIF/tIF) was performed.
on normal mouse brain sections from neonates, postnates and adults (P3, P17 and 3 months, respectively) stained with antisera, anti-BrdU and various markers for NPC characterization. Additionally, in vitro comparative immunoreactivity assessment was performed, where NPCs were challenged with antisera and stained for Caspase 3.

**Results**: Western blot on NPCs substrate indicated specific bands (60,40-46KDa), other than MOG (26-28KDa), when using EAE-AS. dIF of Nestin+/BrdU+, EAE-AS+/BrdU+ and Musashi-1+/BrdU+ revealed abundance of positive cells in all groups: P3; Nestin: 82.30±7.464%; Musashi-1: 78.86±5.851%, P17; Nestin: 77.20±9.476%; Musashi-1: 75.82±4.822% and in 3 months; Nestin: 62.13±7.94%; Musashi-1: 61.26±6.208%. Moreover, tIF of EAE-AS+/BrdU+/SOX-2+ in neonates showed increased colocalization while in EAE-AS+/BrdU+/DCX+ colocalization was remarkably less (78.71±8.325% vs 13.073±3.840%). Additionally, in postnates, SOX-2 diminishes while DCX escalates in adults (Postnates: SOX-2; 45.61±11.78%, DCX; 90.83±3.493%, Adults: SOX-2; 77.45±9.227%, DCX; 100.00±0.0%). Immunocytochemistry of NPCs with Caspase 3 showed increased expression when stimulated with EAE-AS versus NAIVE-AS (Caspase 3; 16.07±1.196% vs 9.554±0.5684% p<0.001).

**Conclusions**: Autoantibodies produced after MOG35-55 immunization exhibit lineage-specific cross reactivity with NPC surface, with variable cell type specificity. Furthermore, autoantibodies have the potential to stimulate apoptotic pathways. These findings indicate that antibody repertoire targets epitopes other than MOG and may lead to functional alteration of NPCs.

**PA19 Kisspeptin: A Key Regulator of Gynecological Endocrinology**

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Kisspeptin, the protein encoded by the KISS1 gene, was initially identified in mammals as a ligand of the G protein-coupled receptor 54, capable of suppressing melanoma and breast cancer metastasis. This protein, along with neurokinin B (NKB) and dynorphin (DYN), is a part of a subgroup of neurons (KNDy), located in the arcuate nucleus of the hypothalamus and plays a crucial role in the activation of the gonadotrophic axis, the puberty onset and the control of reproduction. Specifically, kisspeptin after receiving paracrine stimuli from NKB and inhibitory feedback from DYN, binds to receptors found on the GnRH neurons, thus their activity is stimulated and they in turn, secrete GnRH and trigger downstream events that support reproduction. A systematic review was performed using the International Literature with databases as PubMed. This review focuses on articles published from 2007-2017, with priority given to articles reporting original research, on both human and animal studies. The data demonstrated that KNDy system regulates reproductive function, as its peptides express estrogen and progesterone receptors that transmit the feedback effects of these steroids to GnRH neurons. Current research focuses on the manipulation of the KNDy system, to enhance gonadal sex steroid production in reproductive disorders characterized by reduced LH pulsatility; hence, clinical applications in cases like, hypothalamic amenorrhea (HA) and hypogonadotropic hypogonadism (HH).
are offered. Additionally, kisspeptin therapy greatly contributes to the improvement of In Vitro Fertilization (IVF) technique. Gonadotropic production is stimulated in a more physiological pathway using this type of therapy, which results in a decreased risk of acquiring ovarian hyperstimulation syndrome (OHSS). Moreover, kisspeptin antagonists can act as a more beneficial female contraceptive method, especially in cases that exogenous estrogen is not recommended, as they can reduce follicular development and prevent ovulation. These antagonists can also treat hormone-dependent disorders of reproduction, such as endometriosis, precocious puberty and metastatic prostate tumors. However, abnormalities in the function of the KNDy system, can lead to neuroendocrine defects, like the polycystic ovarian syndrome. Mutations of the KNDy system that result in the problematic signaling of either of these peptides (Kisspeptin, NKB, DYN) influence puberty onset. To conclude, kisspeptin stimulates GnRH neurons, by acting downstream to metabolic signals. Its signaling can activate the gonadotrophic axis, regulate puberty onset, gonadal sex steroid production and metastasis of specific tumors. Additionally, it exhibits clinical applications in cases like HA or HH and kisspeptin therapy is a promising advance that successfully and safely causes oocyte maturation in patients undertaking IVF treatment at high risk of developing OHSS.

PA20 Monitoring lung cancer therapy via liquid biopsy

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Introduction: Liquid biopsy is a non-invasive sample source that can be utilized to assess cancer response to drug therapy by measuring the tumor-derived fraction of circulating cell-free DNA (cfDNA) in plasma.

Purpose: The purpose of this study was to evaluate the clinical significance of liquid biopsy by monitoring the treatment outcome of a patient with lung cancer (NSCLC).

Materials/Methods: Both FFPE and cfDNA samples of this patient were subjected to Accel-Amplicon 56G Oncology Panel which offers comprehensive and hotspot coverage of 56 clinically-relevant oncology-related genes. The runs were conducted on MiSeq platform (Illumina) with MiSeq- 300V2 kit. Liquid biopsy was performed after one week and then after a month of the beginning of a third generation EGFR-TKI treatment (with rociletinib).

Results: The mutation T790M of the EGFR gene was detected in both FFPE and in first cfDNA samples. The T790M mutation levels were slightly decreased after one week and much further after one month of therapy. Therefore, therapy seems to be effective.

Conclusion: Tissue biopsy still represents the gold standard for characterizing the initial
tumor sample, but liquid biopsy seems to be a valuable tool for monitoring patients subjected to therapy.

**PA21**  
**TruSight Enrichment Workflow vs PCR Amplicon Workflow (MASTR) for targeting cancer genes**

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**Introduction:** Breast cancer has been associated with mutations in other low and high penetrant genes except of BRCA. This knowledge allows us to identify more women at risk for breast cancer. The purpose of this study was to compare PCR Amplicon Workflow (BRCA HC MASTR Plus) which detects mutations and CNVs in 26 “breast cancer” genes and TruSight Enrichment Workflow (TruSight cancer) which targets 94 “cancer” genes.

**Materials/Methods:** 30 patients with mild to severe family history were subjected to BRCA HC Plus panel and 12 to the TruSight cancer panel (TC). Three runs were conducted using MiSeq 600V3 reagent kit in the former case, i.e. 10 samples per run, while 4 samples each time were loaded on a MiSeq 300V2 kit, regarding the latter panel.

**Results:** Both panels require a low input of DNA and have an efficient workflow. Regarding hands-on time, it seems that BRCA HC MASTR Plus workflow is shorter and it may be easier for a less experienced user. Considering the quality of the final results, a high Q-score was achieved with both panels. However, the average coverage (read-depth) reached with the former panel was higher i.e. about 500x for most of the targeted genes compared to the one reached with the TC, regarding the common cancer genes.

**Conclusion:** TC panel could be a solution for cases with a rather inconclusive family history, but for patients with a distinct phenotype BRCA HC MASTR plus panel offers a rather more robust and efficient method for confirming diagnosis.
The aim of the present study was to develop an experimental model of Landrace pig hepa
tectomy, in order to study the action of the antioxidant U-74389g (21– amino
teroid) molecule based on the haematodynamic changes and liver biochemistry of
these pigs as well as on the innate and adaptive immunological response of the liver.
The two latest parameters define mostly the nature of the lesions, being either of the
ischemic/reperfusion type or not. Furthermore, the application of the antioxidant
molecule in such cases, has recently been proven to reduce renal injury due to ischemia/
reperfusion in rats.

In order to investigate the effect of the molecule in the liver our histological study included
fourteen Landrace pigs (30 ± 2 Kgr), seven of which received the molecule (experimental
group) after being anesthetized under a specific protocol and after an abdominal inci-
sion by Pringle procedure and a typical left lateral hepatectomy with cross-section and
ligation of the triple portal for liver sections II and III. The animals were awakened and kept
for 24 hours. At 24 hours, the animals were dumped based on the protocol and blood was
collected along with histologic lesions on predefined time periods (before Pringle proce-
dure, after Pringle procedure, 1 hr after hepatectomy and 24 hrs after hepatectomy). The
procedure was then followed by euthanasia of the experimental animals.
Liver biopsies were fixed in a 4% formalin buffer, then embedded in paraffin wax and sec-
tioned in 5μm thick slices, prior to their histochemical staining. The study was performed
quantitatively, by counting the number of inflammatory cells (lymphocytes, neutrophils,
macrophages) and apoptotic bodies, in routine H&E stains, at 400X magnification, using
the Feng L. scale. Histological evaluation revealed the presence of inflammation and
apoptosis, of the same density, both in the untreated (control) and the experimental
group, showing therefore that no impact of the molecule was substantiated, regarding
the liver, up to 120 min after the antioxidant was supplied to the experimental group. A
study on specific inflammatory-related markers in the blood such as the Toll-lile receptor
and Nuclear Factor – kB (NF-kB) will also be performed.
The study was designed to focus on the spectrum of U-74389g molecular actions as an
antioxidant/anti-inflammatory molecule, so as to give an indication for further clinical
studies.
PA23 Bovine miRNA miR-154c can survive digestion and affect human genes in epithelial cells

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Colorectal cancer (CRC) is the second most frequent human cancer with over 1.3 million new cases globally and over half a million deaths per year. The global burden of CRC is expected to increase by 60% by 2030 despite the increased preventing screening efforts. CRC is a complex disease caused by the interaction of both genetic and environmental factors with diet and in particular the high consumption of red meat (especially beef) being a risk factor for CRC initiation.

The current research focused on a novel hypothesis regarding the molecular mechanisms behind the initiation and progression of CRC while also addressing a new, emerging and highly controversial scientific field entitled: “The Dietary XenomiR hypothesis” which, if proven, could have imperative biomedical impact, challenging our current knowledge on the nutrition-disease interconnection.

In this proof-of-principle study we tested whether a selected ingested beef miRNA (namely bovine Mir154-c) has the potential to regulate human genes initiating or adding to the progression of colorectal cancer. Specifically, Mir154-c was selected after bioinformatic filtering and further studied for its “survival” through cooking as well as through human digestion.

Mir154-c was also tested for its effect on human intestinal epithelial cells after transfection. Identification of beef miRNAs as the link between diet and CRC will have implications for prevention, risk-assessment and therapy of an increasingly frequent human cancer while add to the growing and controversial field of “cross-species regulation by dietary miRNA”; a phenomenon that could revolutionize our understanding of the effect of diet on human disease.

PA24 Single-base primer extension (minisequencing) assay for the determination of 7 HBB mutations

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β-thalassaemia is the most common autosomal recessive disorder worldwide, with a carrier frequency of 12% in Cyprus. It can be caused by a variety of mutations within the β-globin gene, leading to reduced or abolished β-globin chain production and consequently to
ineffective erythropoiesis and haemolysis. Early diagnosis of β-thalassaemia is essential in order to proceed with genetic counselling, management and prenatal diagnosis if chosen. Here we present a minisequencing assay for the simultaneous determination of the seven most common β-thalassaemia mutations in Cyprus. In this study, after the optimization of each single-base extended primer for multiplex performance, we analysed 44 samples where we correctly genotyped all of them. These samples were run in parallel using the ARMS methodology where confirmation of the results of the minisequencing assay was obtained. The single-nucleotide primer extension method is a rapid, inexpensive, easy and reliable technology used for the identification of various mutations in a multiplex manner. It has been already introduced into the clinical practise with success, outstanding from other obsolete and time-consuming methods used up until recently.


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The objectives of this study are: (a) to report our experiences of the routine implementation of fetal RHD genotyping by analysis of cell-free fetal DNA extracted from maternal plasma of RhD negative women at risk of haemolytic disease of newborn, (b) to estimate the RhD phenotype frequencies, the RHD genotype frequencies and the RhD zygosity in the Cypriot population.

cffDNA was extracted from maternal plasma of 73 RhD negative pregnant women. Real-Time Multiplex-PCR was used to amplify regions of RHD gene in exons 4, 5 and 10. RhD phenotypes were determined on 445 random samples using conventional agglutination slide test.

The fetus was predicted to be positive in 53 cases and negative in 18 cases. Two cases were identified as D-variants, weak-D type-1 and 11, The frequency of RhD negative homozygosity in the Cypriot population was estimated to be 7.2%, while the frequencies of RHD hemizygosity and RhD positive homozygosity was calculated to be 39.2% and 53.6%, respectively.
Fetal RHD genotyping can be accurately determined using cffDNA from maternal plasma. The implementation of the test has eliminated all use of unnecessary anti-D and reduced the total use of anti-D by 25.3% while achieving appropriate management of the RhD negative pregnancies.

PA26 Amygdalin Extract Promotes Selective Cell Death
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Natural plant extracts have been used for centuries for treating many types of diseases including inflammatory related diseases as well as cancer. One of these extracts is amygdalin which is a natural compound mostly extracted from the seeds of bitter almonds and apricots. Due to its cyanate containing structure, amygdalin has been reported to have anti-tumor properties by promoting apoptosis. In the present study, we treated various cancer cell lines with different doses of amygdalin. Our experiments on cancer cell lines such as Pancreatic, Prostate, Breast and laryngocarcinoma, revealed that treatment with amygdalin results cell death in a dose dependent manner with approximately 75% death in cancer cell lines at a dose of 1 mg/ml.

Moreover, experiments in normal cells like peripheral blood mononuclear cells (PBMC’s) and MCF10A MCF12F (breast cells) shows that amygdalin has no toxic effect. From our results we show that amygdalin may indeed have anti-cancer properties and therefore be a promising therapeutic agent use for cancer treatment.
Non-invasive prenatal testing has revolutionized the field of prenatal diagnosis over the last few years. High-throughput technologies have demonstrated safe, accurate and reliable results for the detection of the most common fetal aneuploidies, fetal sex abnormalities and microdeletion syndromes, relying on the detection and analysis of cell-free fetal DNA (cffDNA) in the maternal plasma. However, such analysis is often limited by the low abundance of DNA, as is the case of fertilized embryos during IVF when subjected to PGS/PGD. Therefore, novel, alternative and sensitive approaches which can provide reliable results from minute amounts of DNA are necessary.

We hereby present a proof of concept study for the robust detection of embryo abnormalities using amplified DNA isolated from 7 and 17 embryos obtained from 3-day and 5-day biopsy cases respectively. All samples were referred for PGS at the Department of Cytogenetics and Genomics at the Cyprus Institute of Neurology and Genetics and subjected to array comparative genomic hybridization (aCGH) as part of the routine screening test. TArgeted Capture Sequences (TACS) were designed at a median resolution of 1Mb spanning all chromosomes and were used to perform in-solution hybridization capture followed by Next Generation Sequencing (NGS) as previously described. Novel bioinformatics algorithms were also developed to determine the ploidy status of the samples. All samples were correctly classified and all abnormalities were detected including numerical and structural rearrangements. Results obtained were in agreement with aCGH results.

As targeted sequencing is the preferred method for applications requiring high read depth, this assay in combination with a novel bioinformatics pipeline will be implemented for the genome-wide screening of fertilized embryos (PGS/PGD) while it can also be leveraged as a tool for disease screening in cases where limited number of cells from affected tissues/individuals are available.


PA28 Preparation and characterization of Nano Naproxen drug: Antioxidant activity and cytotoxicity assay

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**Introduction and aim:** Naproxen is a non-steroidal anti-inflammatory drug that belongs to a variety of groups including phenates, salicylates, propionic acid, etc., and is considered as one of the propionic acid derivatives. It has low water solubility and has low permeability. Because insufficiently soluble and insoluble drugs exhibit low absorption and poor bioavailability, improvements in solubility and solubility are important for developing various drug preparation methods. Like many medications, gastrointestinal tract irritation (GIT) is one of the most important side effects seen with oral naproxen. Therefore, we decided to produce nano-naproxen in this study and produce a capsule for comparison with naproxen drug. Also in this study, antioxidant properties, cell toxicity, naproxen and nano naproxen have been investigated in comparison with naproxen.

**Materials and Methods:** In this study, for the synthesis of nanoparticles, 1 g of powdered drug was distributed in a solvent of water and acetone and uniformized by ultrasonic technique in a hot water bath with a reaction temperature of 30 °C. After 15 minutes of reaction, nano-naproxen was deposited. In the next step, the results of the raw materials from the two drugs and reaction products were investigated by Fourier Infrared (FT-IR) spectroscopy, ultraviolet and visible absorption spectroscopy (UV-Vis) and core magnetic resonance spectrum (NMR). The results of the 1H-NMR and 13C-NMR obtained from the product analysis revealed the binding method of the two drugs and the resulting changes in the structure of the complex. Also, the results of the analysis of the FT-IR and UV-Vis spectra in comparison with the raw materials indicate that this drug was synthesized.

**Results:** The absorption spectra of naproxen and naproxen were encoded by Niosum at a wavelength of 200-800 nm. The main source of absorption of naproxen at 234, 244, 262, 272, 332 nm was wavelengths, while the peak absorption peak of naproxen was encapsulated by Niosum at 234, 272, 318 nm. The Naproxen / PLGA absorption spectrum was at a maximum of 242, 268 nm and had a weak absorption of 322, 328 nm. The use of the Niosum nanocomponent for the transfer of naproxen to the MCF-7 cancer cell has led to a significant increase in the toxicity of naproxen, with half of the cancerous cells killed in the concentration of 10 μM encapsulated naproxen. This makes more sense than free naproxen because it does not have significant toxicity in any of the concentrations and half of the cells have not been killed, No longer has been classified with IC50 concentration.

**Conclusion:** This study suggests that the nanocomposites likely to increase the penetration and effect of the cells significantly and increase solubility.

**Key words:** Nano naproxen, cytotoxicity, Anti-oxidant

**PA29 Time of the Day Dictates the Variability of Biomarkers of Exposure to Disinfection Byproducts**

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Non-persistent environmental chemicals (NOPEC) are xenobiotics with short half-lives of elimination (<7h). Similar to chronopharmacokinetics, NOPEC metabolism may follow diurnal patterns of cytochrome P450 activity. The role of circadian liver clock in shaping NOPEC metabolism and their concomitant measurements of biomarkers of exposure and effect remains poorly understood in real-life human settings. Metabolic activation (toxication) by CYP2E1 converts trihalomethanes (THM) to harmful metabolites. We investigated the diurnal variation of urinary THM exposures and their metabolism patterns as catalysed by CYP2E1 enzyme activity, using the surrogate marker of 4-hydroxynonenal (4HNE). We implemented three time-series trials with adult volunteers conducting specific household cleaning activities at predefined times of a day. Nychthemeral variation of 4HNE was assessed with a cosinor model and its mesor levels increased with THM exposure. The time of exposure within the day dictated the magnitude of urinary THM levels and their toxication effect; in all three trials and relative to urinary THM levels before the activity, lower and higher median THM were measured right after the activity in morning and afternoon/night, respectively. This is consistent with higher reported CYP2E1 activity in light/active phase. Population health studies should incorporate time-stamped biomarker data to improve the understanding of chronic disease processes.

COMPETING FINANCIAL INTERESTS: The authors declare no competing financial interests.

PA30 Tripterygium Wilfordii Promotes Selective Cell Death via a Novel Na/K ATP-ase Pathway
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Presented by: Panayiota Christodoulou
There has been an enormous interest in the literature that phyto-compounds have therapeutic and beneficial effects in various diseases including inflammatory associated arthritis, diabetes, hypertension, parasitic infections, and cancer. A natural extract isolated from leaf and root of the Chinese herb called Tripterygium wilfordii Hook “F” shown to have anti-cancer effects by promoting cancer cell death. The precise target of action for this plant-base anti-cancer agent has not characterized yet. Importantly, studies performed with Tripterygium wilfordii have not indicated whether these anti-cancer plant-base agents have any toxic effects on normal cells. In the present study we show
that Tryptergium extract exposed to different cancer cell lines including HeLa, Pancreatic, Prostate, Breast and laryngocarcinoma caused cell death in a dose-dependent manner, with 85% death in cancer cells at a dose of 1mg/ml. Importantly, Tryptergium extract did not have cell death effects on normal cells (PBMC’s, MCF12F and MCF10A). An in silico approach on the most abundant molecules found in Tripterygium wilfordii indicated a possible association with the Na+/K+ ATPase and this was confirmed with specific in vitro studies. Thus, these results strongly indicated that Tripterygium wilfordii has selective death promoting activity in cancer cells.

PA31  Safe pathway is involved in cardioprotective mechanism of oxytocin post conditioning in isolated rat heart

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Introduction and aim: Oxytocin (OT) has a postconditioning effect against Ischemic-reperfusion (I/R) injury. However, its precise cardioprotection mechanism at early reperfusion phase remains under debate. Our previous study revealed that OT postconditioning is cardioprotective via activation of the reperfusion injury salvage kinase (RISK) pathway. Therefore, the present study aimed to determine the biological effects of OT postconditioning via the OT receptor and the activation of the JAK/STAT3 signaling cascade, mitochondrial adenosine triphosphate dependent potassium channel (mitoKATP), nitric oxide (NO) release and its anti-apoptotic effect against (I/R) injury in an isolated rat heart model.

Materials and Methods: Sixty–three rats were randomly allocated to one of 9 groups. OT was perfused 40 minutes prior to regional ischemia or 15 minutes at the early reperfusion phase. AG490 (a JAK/STAT3 inhibitor), 5HD (a mitoKATP blocker), Atosiban (an OT receptor antagonist) and L-NAME (a nonspecific nitric oxide synthase inhibitor) were applied either alone or in combination with OT during the pre-ischemia or early reperfusion phase. Myocardial infarct size, hemodynamic factors, ventricular arrhythmia, coronary flow, cardiac biochemical marker and the apoptosis index were determined at the end of reperfusion.

Results: OT postconditioning significantly reduced infarct size, lactate dehydrogenase concentrations, arrhythmia score, incidents of ventricular fibrillation and apoptosis. It was also associated with increased coronary flow. Additionally, AG490, 5HD, Atosiban and L-NAME abrogated the cardioprotective effects OT. Our results demonstrated that the cardioprotective effects of OT are mediated via the OT receptor, NO release, activation of the mitoKATP and SAFE pathway through the JAK/STAT3 signaling pathway and reduction of the apoptosis index during the early reperfusion phase.

Keywords: Cardioprotection; Ischemic Postconditioning; Isolated Heart ; Oxytocin; SAFE Pathway; Mitochondrial K(ATP) channel; Nitric Oxide
ITHANET: An information and database community portal for haemoglobinopathies

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The ITHANET Portal (www.ithanet.eu) is an expanding resource for researchers and health care professionals dealing with haemoglobinopathies. As an official partner of the Global Globin 2020 Challenge, an initiative of the Human Variome Project, the ITHANET Portal has been selected for national data collection, storage and sharing, as well as for the development of a thalassaemia-specific genotype-phenotype database. ITHANET has a high-profile international governance structure and its core IthaGenes database, with 2689 fully annotated mutations in 232 globin-related loci and genes, is already the largest disease-specific mutation database for haemoglobinopathies. The ITHANET Portal offers a wide range of resources, as follows:

1. Curated databases and tools (IthaGenes, IthaMaps, IthaChrom):

   a. IthaGenes is a database that organises genes and variations affecting haemoglobinopathies, including causative mutations, disease-modifying mutations and diagnostically relevant neutral polymorphisms. Additionally, IthaGenes integrates the NCBI sequence viewer for detailed graphical representation of each variation and provides phenotype, epidemiology, HPLC data, related publications and external links. Live searches and interactive advanced filters facilitate the retrieval of matching entries.

   b. IthaMaps is a database that stores information on the epidemiology of haemoglobinopathies as documented in published literature and illustrates this information on a dynamic global to regional map. Country-specific information on haemoglobinopathy-related policies, prevalence, incidence and overall disease burden is given, including relative allele frequencies of specific globin mutations in each country and/or region, dynamically linked to corresponding IthaGenes entries.

   c. IthaChrom provides digitised reports (as kindly provided by Bio-Rad Laboratories Inc.) of standard diagnostic high-performance liquid chromatography (HPLC) analyses as a reference tool for haemoglobinopathy diagnosis, allowing database searches of key data.

2. Latest information on haemoglobinopathies, also available by newsletter subscription and covering news, events, publications and clinical trials.

3. A global haemoglobinopathy directory, providing lists of organisations and experts
working in the field of haemoglobinopathies.

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**Disclaimer:** The authors have no conflicts of interest to declare

PA33 LESS MEANS MORE: KNOCKDOWN OF ABERRANT HBBIVSI-110(G>A) mRNA RESTORES HBB EXPRESSION AND ENHANCES GENE THERAPY BY GENE ADDITION IN PRIMARY ERYTHROID CELLS

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**Background:** β-Thalassemias are mostly autosomal recessive disorders caused by mutations in the β-globin gene (HBB). The common HBBIVSI-110(G>A) splicing mutation creates an abnormal splice acceptor site, leading to the incorporation of a 19-nucleotide intronic sequence with an in-frame premature stop codon into the resulting mRNA. Primary erythroid cells from patients with HBBIVSI-110(G>A) are difficult to treat with gene therapy by gene addition, suggesting an effect of the mutant locus on normal, endogenous or vector-encoded, β-globin alleles.

**Aims:** This study aimed to improve gene-addition treatment of HBBIVSI-110(G>A)-homozygous patients, based on the hypothesis that the mutant locus acts in trans by aberrant HBBIVSI-110(G>A)-derived mRNA. For this purpose, RNA interference was utilized in an effort to reduce the latter.

**Methods:** Lentiviral-encoded shRNAs targeting the aberrant HBBIVSI-110(G>A) mRNA were tested alone and in combination with the HBB-encoding GLOBE vector, first, in a novel humanized murine erythroleukemia cell model holding the human HBBIVSI-110(G>A) splice defect and, second, in primary hematopoietic stem and progenitor cells from HBBIVSI-110(G>A)-homozygous patients.

**Results:** The specific knock-down of the aberrant HBBIVSI-110(G>A) mRNA resulted in extremely significant induction of β-globin production both in our humanized murine cell line and in primary patient-derived hematopoietic stem and progenitor cells. In primary cells, β-globin production and phenotypic correction of erythroid-lineage differentiation
were equal to or exceeded that achieved by same-sample control treatment with the clinically successful GLOBE gene-therapy vector. Furthermore, combination of HBBIVSI-110(G>A) knockdown with GLOBE resulted in significant improvement of both disease parameters compared to either treatment alone. **Conclusions:** The results of our novel combinatorial approach are important for mutation-specific gene therapy of β-thalassemia, and emphasize the need to consider allelic heterogeneity in the application of gene therapy by gene addition. Moreover, our shRNA-based strategy might find application in other mutations and disorders associated with aberrant transcripts.

**PA34 Microvessel Density as a Surrogate Prognostic Marker in Patients with Multiple Myeloma: A Meta-Analysis**

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Keywords: Microvessel density · Multiple myeloma · Survival · Meta-analysis  

**Background/Aims:** Bone marrow (BM) angiogenesis is considered crucial for the development and progression of multiple myeloma (MM). Bone marrow angiogenesis can be quantified with the use of microvessel density (MVD). The purpose of this study is to provide a review and a meta-analysis of the current literature regarding the prognostic value of MVD in the overall survival (OS) of MM patients.  

**Methods:** MEDLINE was screened for studies evaluating the OS of MM patients concerning their MVD count in BM trephine. The pooled hazard ratio (HR) and its associated 95% confidence interval (CI) among MM patients with a high and low MVD count was the primary end point. Secondary outcomes included odds ratios (OR) for 12-, 36-, and 60-month survival.  

**Results:** Ten eligible trials were identified for the analysis of the primary end point and 9 for the secondary end points. Pooled HR for OS was 1.85 (95% CI: 1.25–2.73, p = 0.002). The pooled OR of survival were 1.59 (95% CI: 1.02–2.46, p = 0.04) at 12 months, 2.90 (95% CI: 1.68–5.03, p = 0.0001) at 36 months, and 3.42 (95% CI: 2.41–4.85, p < 0.00001) at 60 months, in favor of the low MVD group.  

**Conclusion:** This meta-analysis provides strong evidence that MVD has significant impact on the clinical outcome of MM patients.

**PA35 Magnetic resonance morphometry of the adult normal lumbar intervertebral space**

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Purpose: This study aims to a) quantify and evaluate normal relationships between neighboring spinal units by using MR imaging indices, b) propose an easy to apply and reproduce method of estimating the correct amount of distraction when surgically restoring a collapsed intervertebral disc, based on individualized measurements.

Methods: This is a retrospective cross-sectional MR imaging study in an asymptomatic population of 119 adult subjects, aged 18 to 55. Each of the examinees demonstrated two or more consecutive intervertebral discs classified as Pfirrmann grade I or II. We measured and studied the relationships of disc height index, Dabbs index, Farfan index, disc convexity index and mean and posterior disc height per spinal level by using multiple regression analysis. All measurements were tested for intra- and interobserver agreement by two raters.

Results: All metrics had a statistically significant correlation with the spinal level. Our results were highly reproducible, with excellent inter- and intraobserver agreement and reliability between two raters (ICC=0.992 and 0.994 respectively). Furthermore, we expressed each intervertebral space as a percentage of its adjacent space, introducing the coefficient α factor for every intervertebral space.

Conclusions: Our results suggest that a normal values’ database to refer to during preoperative planning of correction of a degenerated intervertebral disc, is feasible. Our study offers new anatomical and radiological insight in terms of spinal measurements and their potential correlation with current surgical techniques. A new approach for calculating disc space as an expression of its adjacent disc has been introduced, with various potential applications.

PA36 LESS MEANS MORE: KNOCKDOWN OF ABERRANT HBBIVSI-110(G>A) mRNA RESTORES HBB EXPRESSION AND ENHANCES GENE THERAPY BY GENE ADDITION IN PRIMARY ERYTHROID CELLS

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Background: β-Thalassemias are mostly autosomal recessive disorders caused by mutations in the β-globin gene (HBB). The common HBB\[^{IVSI-110(G>A)}\] splicing mutation creates an abnormal splice acceptor site, leading to the incorporation of a 19-nucleotide intronic sequence with an in-frame premature stop codon into the resulting mRNA. Primary erythroid cells from patients with HBB\[^{IVSI-110(G>A)}\] are difficult to treat with gene therapy by gene addition, suggesting an effect of the mutant locus on normal, endogenous or vector-encoded, β-globin alleles.

Aims: This study aimed to improve gene-addition treatment of HBB\[^{IVSI-110(G>A)}\]-homozygous patients, based on the hypothesis that the mutant locus acts in trans by aberrant HBB\[^{IVSI-110(G>A)}\] mRNA. For this purpose, RNA interference was utilized in an effort to reduce the latter.

Methods: Lentiviral-encoded shRNAs targeting the aberrant HBB\[^{IVSI-110(G>A)}\] mRNA were tested alone and in combination with the HBB-encoding GLOBE vector, first, in a novel humanized murine erythroleukemia cell model holding the human HBB\[^{IVSI-110(G>A)}\] splice defect and, second, in primary hematopoietic stem and progenitor cells from HBB\[^{IVSI-110(G>A)}\]-homozygous patients.

Results: The specific knock-down of the aberrant HBB\[^{IVSI-110(G>A)}\] mRNA resulted in extremely significant induction of β-globin production both in our humanized murine cell line and in primary patient-derived hematopoietic stem and progenitor cells. In primary cells, β-globin production and phenotypic correction of erythroid-lineage differentiation were equal to or exceeded that achieved by same-sample control treatment with the clinically successful GLOBE gene-therapy vector. Furthermore, combination of HBB\[^{IVSI-110(G>A)}\] knockdown with GLOBE resulted in significant improvement of both disease parameters compared to either treatment alone.

Conclusions: The results of our novel combinatorial approach are important for mutation-specific gene therapy of β-thalassemia, and emphasize the need to consider allelic heterogeneity in the application of gene therapy by gene addition. Moreover, our shRNA-based strategy might find application in other mutations and disorders associated with aberrant transcripts.

PA37 Gene Correction at Clinically Relevant Efficiencies by Non-viral Delivery and Disruption of an Aberrant Regulatory Element

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The rapidly evolving field of genome-editing has raised hopes for the permanent therapy of a plethora of human diseases. However, most of the correction approaches are based on homologous recombination and suffer from low efficiencies, impeding their progress to clinical trials.

In this study, we established a novel mutation-specific approach for the correction of missplicing by disruption of aberrant regulatory elements (DARE), exploiting the common and efficient non-homologous-end joining repair mechanism (NHEJ). One of the commonest β-thalassaemia mutations in most Mediterranean and many Western countries, HBB-VS1-110(G>A), was used as a missplicing mutation model to test the DARE strategy. This mutation exemplifies more than 180 known disease-causing mutations suitable for DARE-based gene correction, while posing a particular challenge through its close proximity to normal regulatory and coding sequences of the HBB gene.

In order to correct the HBB-VS1-110(G>A) mutation we developed and characterized efficient RNA-guided (RGEN) and TAL effector (TALEN)-based mutation-specific nucleases. Proof of principle of correction by DARE was achieved by plasmid-based nuclease expression in humanized transgenic HBB-VS1-110(G>A) cell lines with TALENs proving superior to RGEN. Initial evaluation of DARE in this model, including clonal analyses, exhibited efficient restoration of correct splicing at the RNA and protein level and highlighted the importance of the flanking regulatory sequences for the recognition of the aberrant splice acceptor site. For analyses in patient-derived CD34+ cells, optimized delivery by nucleofection of in vitro synthesized mRNA and ribonucleoprotein for TALENs and RGEN, respectively, reached exceptionally high bulk disruption efficiencies of up to 90%. Restoration of correct splicing established HBB expression relative to normal controls of between 38.1% and 68.2% for TALENs and 57.1% and 82.6% for RGEN. Through particular design features, i.e. specific TALEN dimer spacer size and a HBB-specific target sequence for the RGEN recognition sequence, off-targeting of the highly sequence-similar HBD paralog was minimal to undetectable. Across all patients, editing achieved significant correction of globin-chain synthesis and of late-stage erythroid differentiation as two hallmarks of β-thalassaemia pathology.

Our study shows that mutation-specific gene therapy by DARE is highly efficient and holds great potential for many human diseases caused by aberrant regulatory motifs. It moreover points out design features that help avoid off-targeting in the presence of close paralogs. Finally, the high level of correction achieved without enrichment, the low level of off-targeting and the use of virus- and DNA-free delivery in primary CD34+ HBB-VS1-110(G>A) cells in this study demonstrate biosafety and efficiency of the established system suitable for direct clinical translation.
PA38 Cadaveric dissection versus plastic models and 3D anatomy computer software: Which is the best method for teaching human upper limb musculoskeletal anatomy?

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Purpose: To examine which method is best for teaching human upper limb musculoskeletal anatomy, when comparing training with dissection of cadavers to the use of plastic anatomy models and 3D anatomy computer software.

Materials and methods: The study was conducted in two consequent semesters. Overall, four groups of 1-year medical students of the University of Thessaly, without previous knowledge of anatomy, were compared. In the first group, 20 students were trained in the anatomy of the upper limb using lectures and cadaver dissection in the lab. In the second group, 15 students were trained using the same means except for the cadaver dissection, which was replaced by the study of plastic anatomy models. In the second semester, two more groups were compared. The first group (41 students) was trained using cadaveric dissection and the second group (32 students) using a 3D computer anatomy program. An anonymous examination was held after the end of the educational process. All students also fulfilled an anonymous questionnaire, evaluating their method of training. Anova and bonferoni t-test were used for the statistical analysis.

Results: Students trained with 3D computer software had a better performance in the exams comparing to students using dissection (p=0.004) and plastic models (p<0.001). Additionally, dissection seems to have a marginal superiority as a training method comparing to plastic models (p=0.051), based on students' performance in the examinations.

Discussion: 3D computer programs seem to be more efficient from both dissection and plastic models. Dissection is still the most commonly used and most preferred method of training.

Conclusion: 3D computer programs can be used for teaching human upper limb musculoskeletal anatomy with better results compared to dissection and plastic models. New technologies, such as 3D anatomy computer programs are gaining popularity and seem to be efficient enough to be used as a part of a typical medical education curriculum.

PA39 DIFERENTIAL DNA METHYLATION PATTERNS OF NEURAL GENE PROMOTERS IN NEURAL PRECURSOR CELLS (NPCs) AFTER CYTOKINE STIMULATION

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Background: NPCs are characterized by their ability to differentiate towards neurons and glia and thus provide a valuable tool in stem cell-based therapies for neurodegenerative...
diseases. However, the inflammatory environment of the CNS seems to affect important biological processes of endogenous or transplanted NPCs. Epigenetic modifications constitute a major intracellular mechanism that controls gene expression in response to extracellular cues. In this context, we aimed to investigate the effects of cytokines, the main inflammatory mediators, on expression levels of differentiation-related genes and also on DNA methylation patterns of the corresponding promoter regions.

**Methods:** NPCs from postnatal C57bl/6 mice were cultured as free-floating neurospheres. Cells were treated with pro- or anti-inflammatory cytokines (IFNγ, TNFα, TGFβ) or vehicle, as control. Total RNA was isolated and reversely transcribed into cDNA. Real time PCR was used to evaluate mRNA expression levels of neural and glial genes. Also, genomic DNA was isolated from each group and was treated with bisulfite. PCR was used for the amplification of selected gene promoter regions. Finally, PCR products were cloned into pCR2.1 plasmids and analyzed with Sanger sequencing.

**Results:** Pro-inflammatory cytokines upregulated proneural and neural gene expression levels. However, they suppressed the expression of glial genes. Among the examined gene promoters, neurogenin-1 (Ngn1) and beta-tubulin III (Tubb3) showed altered DNA methylation patterns after cytokine stimulation (Ngn1: ctrl-5%, IFNγ-4.2%, TNFα-3.05%, TGFβ-4.1%, Tubb3: ctrl-88.3%, IFNγ-92.3%).

**Conclusions:** Pro-inflammatory environment of the CNS affects NPCs differentiation potential, inducing neuronal lineages and simultaneously suppressing glial differentiation. Our results indicate that the induction of neural gene expression could be regulated via DNA methylation.

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**PA40 SAFE pathway is involved in cardioprotective mechanism of oxytocin postconditioning in isolated rat heart**

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Oxytocin (OT) has a postconditioning effect against Ischemic-reperfusion (I/R) injury. However, its precise cardioprotection mechanism at early reperfusion phase remains under debate. Our previous study revealed that OT postconditioning is cardioprotective via activation of the reperfusion injury salvage kinase (RISK) pathway. Therefore, the present study aimed to determine the biological effects of OT postconditioning via the OT receptor and the activation of the JAK/STAT3 signaling cascade, mitochondrial adenosine triphosphate dependent potassium channel (mitoKATP), nitric oxide (NO) release and its anti-apoptotic effect against (I/R) injury in an isolated rat heart model.
Sixty–three rats were randomly allocated to one of 9 groups. OT was perfused 40 minutes prior to regional ischemia or 15 minutes at the early reperfusion phase. AG490 (a JAK/STAT3 inhibitor), 5HD (a mitoKATP blocker), Atosiban (an OT receptor antagonist) and L-NAME (a nonspecific nitric oxide synthase inhibitor) were applied either alone or in combination with OT during the pre-ischemia or early reperfusion phase. Myocardial infarct size, hemodynamic factors, ventricular arrhythmia, coronary flow, cardiac biochemical marker and the apoptosis index were determined at the end of reperfusion. OT postconditioning significantly reduced infarct size, lactate dehydrogenase concentrations, arrhythmia score, incidents of ventricular fibrillation and apoptosis. It was also associated with increased coronary flow. Additionally, AG490, 5HD, Atosiban and L-NAME abrogated the cardioprotective effects OT.

Our results demonstrated that the cardioprotective effects of OT are mediated via the OT receptor, NO release, activation of the mitoKATP and SAFE pathway through the JAK/STAT3 signaling pathway and reduction of the apoptosis index during the early reperfusion phase.

Keywords: Cardioprotection; Ischemic Postconditioning; Isolated Heart; Oxytocin; SAFE Pathway; Mitochondrial K(ATP) channel; Nitric Oxide

PA41 Single-base primer extension (minisequencing) assay for the determination of 7 HBB mutations

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β-thalassaemia is the most common autosomal recessive disorder worldwide, with a carrier frequency of 12% in Cyprus. It can be caused by a variety of mutations within the β-globin gene, leading to reduced or abolished β-globin chain production and consequently to ineffective erythropoiesis and haemolysis. Early diagnosis of β-thalassaemia is essential in order to proceed with genetic counselling, management and prenatal diagnosis if chosen.

Here we present a minisequencing assay for the simultaneous determination of the seven most common β-thalassaemia mutations in Cyprus. In this study, after the optimization of each single-base extended primer for multiplex performance, we analysed 44 samples where we correctly genotyped all of them. These samples were run in parallel using the ARMS methodology where confirmation of the results of the minisequencing assay was obtained. The single-nucleotide primer extension method is a rapid, inexpensive, easy and reliable technology used for the identification of various mutations in a multiplex manner. It has been already introduced into the clinical practise with success, outstanding from other obsolete and time-consuming methods used up until recently.
Prevalence of RhD Status and Clinical Application of Non-Invasive Prenatal Determination of Fetal RHD in Maternal Plasma: a 5 Year Experience in Cyprus.

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The objectives of this study are: (a) to report our experiences of the routine implementation of fetal RHD genotyping by analysis of cell-free fetal DNA extracted from maternal plasma of RhD negative women at risk of haemolytic disease of newborn, (b) to estimate the RhD phenotype frequencies, the RHD genotype frequencies and the RhD zygosity in the Cypriot population.

cffDNA was extracted from maternal plasma of 73 RhD negative pregnant women. Real-Time Multiplex-PCR was used to amplify regions of RHD gene in exons 4, 5 and 10. RhD phenotypes were determined on 445 random samples using conventional agglutination slide test.

The fetus was predicted to be positive in 53 cases and negative in 18 cases. Two cases were identified as D-variants, weak-D type-1 and 11, The frequency of RhD negative homozygosity in the Cypriot population was estimated to be 7.2%, while the frequencies of RHD hemizygosity and RhD positive homozygosity was calculated to be 39.2% and 53.6%, respectively.

Fetal RHD genotyping can be accurately determined using cffDNA from maternal plasma. The implementation of the test has eliminated all use of unnecessary anti-D and reduced the total use of anti-D by 25.3% while achieving appropriate management of the RhD negative pregnancies.
PA43 Spinal cord expression of Stathmin-1, SCLIP and SCG10 in Experimental Autoimmune Encephalomyelitis

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Background: The role of stathmins is the regulation of microtubule equilibrium and cytoskeleton reorganization. They alternate between assembly and disassembly of the cell with the purpose of correct formation of mitotic spindle.

Objective: We studied the stathmin expression in the spinal cord in EAE.

Material and Methods: EAE mice were examined at three time-points (D10, acute, chronic) and compared with controls (D0). Stathmin1, SCG10 and SCLIP mRNA and protein expression was studied using Real Time-PCR and optical and confocal microscopy.

Results: There was reduced mRNA expression in acute phase of stathmin1 (p< 0.05); SCLIP was reduced both in acute and chronic phase of EAE (p< 0.01). An overall decrease of spinal cord stathmin1 and SCG10 protein expression was noticed in acute phase (p< 0.001, p< 0.05). However, our sub-analysis in the inflamed white matter showed increased expression of all stathmins (p< 0.05, p< 0.001,p< 0.01). Moreover, Stathmin1 was predominantly expressed in NG2+ (p< 0.001) and O4+ (p< 0.05) cells whereas in lower levels in CNPase+ (p< 0.05) cells during the acute phase. SCG10 and SCLIP were expressed in axons already during the acute phase and throughout the entire EAE course though not in controls. In addition, inside the inflammatory lesions SCG10 was co-expressed with APP (p< 0.05), a marker of acute axonal damage whereas SCLIP followed the opposite course and was co-expressed with GAP-43(p< 0.05), a marker of axonal regeneration.

Conclusions: The stathmin protein family kinetic in inflammatory demyelinating areas indicates their potential involvement in the underlying pathology and reorganization of the degenerative spinal cord during EAE.
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