

Discovery of novel prophylactic pharmacological interventions against anti-tumor drugs cardiovascular adverse effects.



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Precision medicine has led to the discovery of novel anti-tumor agents against various malignancies. Despite the fact that patient survival steadily increases, a concomitant increase in cardiovascular adverse effects from anti-tumor agents is also observed. Cardio-oncology, aims into identifying the exact pathomechanisms of the aforementioned cardiovascular toxicities and providing novel therapeutic regimens for their management, without hindering the antitumor potential of the anti-tumor therapies. Since the identification of doxorubicin cardiomyopathy up to the recently recognized irreversible proteasome inhibitor, carfilzomib, induced cardiomyopathy, our laboratory specializes in establishing translational models of cardiotoxicity and subsequently proposes translational and clinically applicable pharmacological interventions against the observed cardiovascular moieties. Our research has proposed the cardioprotective potential of phytochemicals such as Oleuropein and inotropes such as Levosimendan in countering doxorubicin cardiotoxicity, as well as it has established a

novel translational model of carfilzomib-cardiotoxicity, in which AMPK α -activator metformin was found to exert prophylactic potential. Our scientific interest focuses on the identification of the precise molecular fingerprint of the cardiotoxicities for the discovery of novel prophylactic therapies, as well as extents in novel anti-tumor agents with proven cardiotoxic effects, such as the lately approved immune checkpoint inhibitors.

SHORT BIOGRAPHY

EDUCATION

- 1988 Degree in Pharmacy, Aristotle's University of Thessaloniki.
- 1994 PhD in Medicinal Chemistry Aristotle's University of Thessaloniki.
- 1994-1996 Post-doctoral training (Leiden Amsterdam Center for Drug Research, Vrije Universiteit Amsterdam, Div. of Molecular Toxicology).
- PhD Thesis: Synthesis of novel anti-inflammatory compounds with basic character: correlation of structural characteristics with activity upon free radicals, drug metabolism and inflammation.
- PostDoc Thesis: Mechanism based design of novel Se-substituted selenocysteine derivatives as potential kidney selective prodrugs.

LANGUAGES

ENGLISH (Proficiency -Central London College), May 1982.

SPANISH Basic knowledge

FELLOWSHIPS

- 1988-1991 State Scholarship Foundation, Athens (Greece)
- 1994 Human Capital and Mobility (Leiden, the Netherlands)
- 1995 European Science Foundation (Strasbourg France)
- 2009 Hellenic Society of Cardiology (Greece). THE HATTER CARDIOVASCULAR INSTITUTE, Research Department of Cardiovascular Medicine, Division of Medicine, University College London Hospital & Medical School- February-March 2009.

RESEARCH AND PROFESSIONAL CAREER

1. 21/07/2020: Profesor of Pharmacology, Pharmaceutical Chemistry Division, School of Pharmacy, National and Kapodistrian University of Athens.
2. 01/09/2016: Associate Prof. of Pharmacology, Pharmaceutical Chemistry Division, School of Pharmacy, National and Kapodistrian University of Athens.

3. 09/12/2011: Assistant Prof. of Pharmacology, Pharmaceutical Chemistry Division, School of Pharmacy, National and Kapodistrian University of Athens.
4. 2006-2011: Lecturer of Pharmacology, Pharmaceutical Chemistry Division, School of Pharmacy, National and Kapodistrian University of Athens.
5. 2003-2006: Teaching Associate, School of Pharmacy, National and Kapodistrian University of Athens.
6. 2005-2016: Research fellow, B' University Dept. of Cardiology, Medical School, National and Kapodistrian University of Athens, Attikon General Hospital, Athens.
7. 2003-2006: Research fellow, B' Anaesthesiology Clinic, Medical School, National and Kapodistrian University of Athens.
8. 2000-2005: Research fellow, B' Cardiology Clinic, Onassis Cardiac Surgery Center.
9. 2000-2006: Postdoc Researcher, Pharmaceutical Chemistry Division, School of Pharmacy, National and Kapodistrian University of Athens.
10. CLINICAL TRIALS: 1998-2005 Clinical Research Associate Manager INTERACT (International Academic Coordination of Trials):
EUROPA 1/1/1998 -30/12/2003: European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery (EUROPA) disease.
PERFECT: Sub-study: PERindopril-Function of the Endothelium in Coronary Artery Disease Trial
PERSPECTIVE: Perindopril's prospective effect on coronary atherosclerosis by angiography and intravascular ultrasound evaluation.
SOTI: The Spinal Osteoporosis Therapeutic Intervention (SOTI): Strontium ranelate: short- and long-term benefits for post-menopausal women with osteoporosis.
TROPOS: Strontium Ranelate Reduces the Risk of Nonvertebral Fractures in Postmenopausal Women with Osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study.
PREAMI 5/2000 - 12/2003: Perindopril and Remodelling in Elderly with Acute Myocardial Infarction.
CARISA 3/2000-2005: A double-blind, randomized, stratified, placebo-controlled, parallel study of Ranolazine SR at doses of 750 mg twice a day and 1000 mg twice a day in combination with other anti-anginal medications in patients with chronic stable angina pectoris.

11.2/1996 -12/1997: ELPEN PHARMACEUTICAL COMPANY, RESEARCH & DEVELOPMENT DEPARTMENT

Objectives:

11.1. Expert report writing (clinical and toxicological expert reports) and supervision of scientists (medical doctors and pharmacists) for expert report writing for the submission of new products in National Organization for Medicines (Part III and IV) and for drug exportation.

11.2. Writing of the Part I for the submission of new products in National Organization for Medicines: Summary Product Characteristics, and User Package Leaflet.

12. 2/1994 - 12/1995, Leiden Amsterdam Center for Drug Research, Vrije Universiteit Amsterdam, Dept. of Pharmacochimistry, Div. of Molecular Toxicology.

Postdoctoral researcher by obtaining fellowships from EU (Human Capital and Mobility, και European Science Foundation) under the supervision of Prof. Nico P.E. Vermeulen.

13. 12/1988- 01/1994, Aristotle's University of Thessaloniki, Department of Pharmacy. PhD fellow from scholarship obtained by State Scholarship Foundation, Athens (Greece) under the supervision of Prof. Panos Kourounakis.

LIST OF RESEARCH GRANTED PROJECTS (last 7)

1. "Development of an innovative- "scientific" intelligent- nutraceutical based on Olive constituents for patients with coronary artery disease and metabolic syndrome", Action "RESEARCH - CREATE - INNOVATE", Operational Programme Competitiveness, Entrepreneurship and Innovation 2014-2020 (EPAnEK), Principal investigator, 2019-2021.

2. "Investigating the mechanisms of Carfilzomib-induced myocardial dysfunction in animal models with comorbidities", Amgen Agreement 6289826, Principal investigator, 2019-2021.

3. "Development of an "intelligent" food supplement based on beetroot and rocket for the improvement of athletic performance and for the limitation of metabolic syndrome symptoms", Action "RESEARCH - CREATE - INNOVATE", Operational Programme Competitiveness, Entrepreneurship and Innovation 2014-2020 (EPAnEK), Co-investigator, 2020-2022.

4. Onassis Foundation, Scholarship of the PhD student P.E. Nikolaou, entitled, "Investigation of cardiac dysfunction in hematological dyscracias and amyloidosis", Onassis Foundation - Scholarship ID: G ZO 020-1/2018-2019.

5. ELIDEK, Scholarship of the PhD student P.E. Nikolaou, entitled “Investigation of cardiac dysfunction in hematological dyscrasias and amyloidosis”, Principal investigator, 2019-2022.
6. “Development and pharmacological evaluation of a natural extract for menopause flushings”, Kleon Tsetis Foundation Scientific Research & Culture, Principal investigator, 2020.
7. “Metabolomic and proteomic investigation of the cardioprotective effect of sodium - glucose co-transporters 2 (SGLT-2) in healthy mice”. Hellenic Society of Cardiology, Principal investigator, 2020-2022.

MEMBERSHIP OF SCIENTIFIC COMMITTEES

1. Vice Chair of the Hellenic Society of Basic and Clinical Pharmacology, (2019).
2. Member of the Administration Board of the Working Group of Cardiomyopathies, Basic Research and Inherited Heart Diseases. (Hellenic Society of Cardiology).
3. Member of the Hellenic Hematological Society (Department of plasmacellular dyscrasias), November 2019.
4. European Cardiology Society, Working Group: Cardiovascular Pharmacology, 2010.
5. Member of ISHR (International Society for Heart Research), 2015.
6. Member of Hellenic Society of Atherosclerosis, January 2019.
7. Membership of the Administration Board of the Hellenic Society of Pharmacoshemistry (Member of European Federation of Medicinal Chemistry, and Member of EUFEPS), 1998-2008.
8. Hellenic Society of Pharmacists, 1998.
9. Hellenic Society of Pharmaceutical Medicine (ELEFI), 1998.
10. Hellenic Pharmaceutical Society (EFE), 2000.

EDITORIAL BOARD MEMBER

- British Journal of Pharmacology
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- Conditioning Medicine
<http://www.conditionmed.org/Data/List/Editorial%20Board>

Publications (2020)

1. A. Lazou, I. Ikonomidis, M. Bartekova, T. Benedek, G. Makavos, D. Palioura, H. Cabrera Fuentes, I. Andreadou*. Chronic inflammatory diseases, myocardial function and cardioprotection. *Brit J Pharmacol*, 2020 Jan 13. doi: 10.1111/bph.14975. (IF: 7.73)
2. C. Penna, I. Andreadou, M. Aragno, C. Beauloye, L. Bertrand, A. Lazou, I. Falcão-Pires, R. Bell, C.J. Zuurbier, P. Pagliaro, D.J. Hausenloy. Effect of hyperglycaemia and diabetes on acute myocardial ischaemia-reperfusion injury and cardioprotection by ischaemic conditioning protocols. *Br J Pharmacol* 2020 Jan 27. doi: 10.1111/bph.14993. (IF: 7.73) (Citations 1)
3. I. Ikonomidis, K. Katogiannis, E. Kyriakou, M. Taichert, G. Katsimaglis, M. Tsoumani, I. Andreadou, E. Maratou, V. Lambadiari, F. Kousathana, A. Papadopoulou, C. Varlamos, P. Plotas, J. Parissis, K. Stamatelopoulos, D. Alexopoulos, G. Dimitriadis, A.E. Tsantes. β -Amyloid and mitochondrial-derived peptide-c are additive predictors of adverse outcome to high-on-treatment platelet reactivity in type 2 diabetics with revascularized coronary artery disease. *J Thromb Thrombolysis*, 2020 Feb 12. doi: 10.1007/s11239-020-02060-4. (IF: 2.054)
4. I. Andreadou, R. Schulz, A. Papapetropoulos, B. Turan, K. Ytrehus, P. Ferdinandy, A. Daiber, F. Di Lisa. The role of mitochondrial reactive oxygen species, NO, and H₂S in ischemia/reperfusion injury and cardioprotection. *J Mol Cell Med*, 24:6510-6522, DOI: 10.1111/jcmm.15279. (IF: 4.486) (Citations 2)
5. C.J. Zuurbier, L. Bertrand, C.R. Beauloye, I. Andreadou, M. Ruiz-Meana, N.R. Jespersen, D. Kula-Alwar, H.A. Prag, H.E. Botker, M. Dambrova, C. Montessuit, T. Kaambre, E. Liepinsh, P.S. Brookes, T. Krieg. Cardiac Metabolism as Driver and Therapeutic Target of Cardiac Infarction. *J Mol Cell Med*, 24:5937-5954, DOI: 10.1111/jcmm.15180. (IF: 4.486) (Citations 1)
6. I. Ikonomidis, G. Pavlidis, J. Thymis, D. Birba, A. Kalogeris, F. Kousathana, A. Kountouri, K. Balampanis, J. Parissis, I. Andreadou, K. Katogiannis, G. Dimitriadis, A. Bamias, E. Iliodromitis, V. Lambadiari. Effects of glucagon like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors and their combination on endothelial glycocalyx, arterial function, and myocardial work index in patients with type 2 diabetes after 12-month treatment *JAHA: Journal of the*

American Heart Association, 5;9(9): e015716, 2020. doi: 10.1161/JAHA.119.015716 (IF: 4.605)
(Citations 2)

7. I. Andreadou*, R. M. Bell, H.E. Bøtker, C.J. Zuurbier. SGLT2 inhibitors reduce infarct size in reperfused ischemic heart and improve cardiac function during ischemic episodes in preclinical models. *BBA - Molecular Basis of Disease*, 1866(7):165770, 2020. doi: 10.1016/j.bbadis.2020.165770. (IF: 4.352) (Citations 2)

8. P.E. Nikolaou, P. Efentakis, F. Abu Qourah, S. Femminò, M. Makridakis, Z. Kanaki, A. Varela, M. Tsoumani, C.H. Davos, C.A. Dimitriou, A. Tasouli, G. Dimitriadis, N. Kostomitsopoulos, C.J. Zuurbier, A. Vlahou, A. Klinakis, M.F. Brizzi, E.K. Iliodromitis, I. Andreadou*. Chronic Empaglifozin treatment reduces myocardial infarct size in healthy mice through STAT-3 mediated protection on microvascular endothelial cells and reduction of oxidative stress. *Antioxidant & Redox Signaling*, doi: 10.1089/ars.2019.7923. (IF: 6.323)

9. I. Ikonomidis, K. Katogiannis, G. Kostelli, K. Kourea, E. Kyriakou, A. Kypraiou, M. Tsoumani, I. Andreadou, V. Lambadiari, P. Plotas, I. Thymis, A.E. Tsantes. Effects of electronic cigarette on platelet and vascular function after four months of use. *Food Chem Toxicol*, 141:111389, 2020. doi: 10.1016/j.fct.2020.111389. (IF: 4.679) (Citations 1)

10. P. Efentakis, H. Doerschmann, C. Witzler, S. Siemer, P.E. Nikolaou, E. Kastritis, R. Stauber, M.A. Dimopoulos, P. Wenzel, I. Andreadou*s, E. Terpos. Investigating the Vascular Toxicity Outcomes of the Irreversible Proteasome Inhibitor Carfilzomib. *Int J Mol Sci*, 21(15):5185, 2020. doi: 10.3390/ijms21155185. (IF: 4.556)

11. I. Ikonomidis, G. Pavlidis, P. Katsimbri, V. Lambadiari, J. Parissis, I. Andreadou, M. Tsoumani, D. Boumpas, D. Kouretas, E. Iliodromitis. Tocilizumab improves oxidative stress and endothelial glycocalyx: A mechanism that may explain the effects of biological treatment on COVID-19. *Food Chem Toxicol* 145:111694, 2020. doi: 10.1016/j.fct.2020.111694. (IF: 4.679)