COST Action CA20121

8th BenBedPhar Scientific Meeting

Thirty years since the discovery of NRF2

10-11 October 2024

"NOVA Medical School Research"
Rua Câmara Pestana 6, 1150-082
Lisbon, Portugal

For: Members of the Management Committee and Work Groups of the COST Action CA20121

NOVA Medical School
NOVA University of Lisbon,
Lisbon, Portugal

Thursday, October 10

08:30 – 09:00 Registration

09:00 – 13:00 **Management Meeting** (*MC members only*)

13:00 – 14:00 Lunch

14:00 – 15:30 **Session 1: New Therapeutic Approaches Involving NRF2**
Chairs: *Gina Manda, Romania, and Margarida Pedro, Portugal*

14:00 – 14:15 **O.01 | Unexpected cytotoxicity of Geldanamycin-based Heat Shock Protein 90 (HSP90) inhibitors in the context of NAD(P)H:Quinone Oxidoreductase 1 (NQO1) deficiency**
Albena T Dinkova-Kostova
University of Dundee, United Kingdom

14:15 – 14:30 **O.02 | Endothelial miR-34a deletion guards NRF2 KO mice against aneurysm development**
Anna Grochot-Przeczek
Faculty of Biochemistry Biophysics and Biotechnology, Jagiellonian University, Poland

14:30 – 14:45 **O.03 | A preclinical approach to explore the NRF2 pathway as a therapeutic strategy in age-related macular degeneration**
Miguel Seabra
NOVA Medical School, UNL Lisboa, Portugal

14:45 – 15:00 **O.04 | Quinolyl nitrone derivative protect from auditory cell oxidative damage and noise-induced hearing loss**
Isabel Varela Nieto
Universidad Autónoma de Madrid, Spain

15:00 – 15:15 **O.05 | Bile acids as immunomodulators and NRF2 activators**
Djordje Miljkovic
IBISS, University of Belgrade, Serbia

15:15 – 15:30 **O.06 | Interplay between NRF2, AQP3 and AQP5 in breast cancer: A pathway to therapy resistance?**
Ana Čipak Gašparović
Ruđer Bošković Institute, Croatia

15:30 – 16:45 Coffee break and **Poster Session (Odd numbers)**

16:45 – 18:00 **Session 2: NRF2 and Inflammation**
Chairs: *Andreas Daiber, Germany, and Marisa Antunes, Portugal*

16:45 – 17:00 **O.07 | NRF2/HO-1 pathway regulates the anti-oxidant and anti-inflammatory response in UVB-exposed primary human keratinocytes**
Agnes Klar
Tissue Biology Research Unit, University of Zurich, Switzerland

17:00 – 17:15 **O.08 | Anti-inflammatory and cytoprotective actions of HYCOs, NRF2 activators that simultaneously release carbon monoxide**
Roberta Foresti
University Paris est Créteil, France

17:15 – 17:30 **O.09 | Possible role of P2X7 on NLRP3 inflammasome regulation by NRF2/DJ-1 pathway stimulation in diabetic nephropathy**
Santiago Cuevas
BioMedical Research Institute of Murcia (IMIB-Arrixaca), Murcia, Spain

17:30 – 17:45 **O.10 | Lupeol modulates redox homeostasis and mitigates oxysterol-induced dysfunction in monocyte-derived dendritic cells via NRF2 pathway activation**
Brigitta Buttari
Istituto Superiore di Sanità, Rome, Italy

17:45 – 18:00 **O.11 | Oxidative lipid alterations and NRF2: Implications for synaptic preservation in Alzheimer's disease**
Ana Isabel Rojo Sanchís
Universidad Autónoma de Madrid, Spain

18:15 **Guided visit to NMS Faculty building**

Friday, October 11

09:30 – 11:00 **Session 3: New Tools and Drug Discovery Targeting NRF2**
Chairs: *Christina Morgenstern, Austria, and Rohini Srivastava, UK*

09:30 – 09:45 **O.12 | NRF2 modulators landscape: Patent challenges and strategies for improving accessibility**
Michel Mickael
IGHZ Institute of Genetics and Animal Biotechnology's, Poland

09:45 – 10:00 **O.13 | NetRF2: A novel pipeline for network-based analysis of NRF2, and its targets, interactions, variants and expressions**
Ozlen Konu
Bilkent University, Turkey

10:00 – 10:15 **O.14 | Carbon nano-onions for targeted drug delivery**
Silvia Giordani
Dublin City University, Irland

10:15 – 10:30 **O.15 | How to study NRF2 isoforms?**
Alicja Sznarkowska
University of Gdansk, International Centre for Cancer Vaccine Science, Poland

10:30 – 10:45 **O.16 | NRF2 and BCL-2 family proteins**
Monika Jakubowska
Jagiellonian University in Krakow, Poland

10:45 – 11:00 **O.17 | Novel small molecules and peptidomimetics inhibitors of NRF2-KEAP1 determined via structure-based virtual screening**
Kemal Yelekci
Kadir Has University, Turkey

11:00 – 11:30 Coffee break

11:30 – 13:00 **Session 4: NRF2 and Oxidative Stress**
Chairs: *Roberto Motterlini, France, and Biljana Miova, Macedonia*

11:30 – 11:45 **O.18 | Proteome and redox instability as major drivers and hallmarks of aging**
Ioannis Trougakos
National and Kapodistrian University of Athens, Greece

11:45 – 12:00 **O.19 | Hypothermia's molecular mechanisms and the role of the antioxidative system**
Kattri-Liis Eskla
University of Tartu, Estonia

12:00 – 12:15 **O.20 | Dissecting NRF2 activation by physiological levels of hydrogen peroxide**
Dina Dikovskaya
University of Plymouth, United Kingdom

12:15 – 12:30 **O.21 | Laminin-α2 chain deficiency leads to multi-organ oxidative stress**
Susana G. Martins
cE3c, FCUL, Portugal

12:30 – 12:45 **O.22 | 30 Years of NRF2: Charting sustainable pathways for the future of the BenBedPhar Action**
Theo Zacharis
Greek Scientists Society, Greece

12:45 – 13:00 **O.23 | Pharmacologic and genetic activation of NRF2 confers anti-fibrotic effects**
Sharadha Dayalan Naidu
University of Dundee, United Kingdom

13:00 – 14:30 Lunch and **Poster Session (Even numbers)**

14:30 – 16:00 **Session 5: NRF2 and Brain Diseases**
Chairs: *Marzia Perluigi, Italy, and Bayram Yilmaz, Turkey*

14:30 – 14:45 **O.24 | Bdnf-NRF2 crosstalk in depression disorder**
Marlene Santos
Escola Superior de Saúde, *Instituto Politécnico do Porto, Portugal*

14:45 – 15:00 **O.25 | Isothiocyanates for protection against neurodegenerative diseases**
Antonio Cuadrado
Universidad Autónoma de Madrid, Spain

15:00 – 15:15 **O.26 | Targeting Alzheimer´s disease hallmarks with the NRF2 activator Isoeugenol**
Maria Teresa Cruz
University of Coimbra, Portugal

15:15 – 15:30 **O.27 | A novel protein-protein NRF2 inducer with anti-neuroinflammatory effects**
Manuela Garcia Lopez
Universidad Autónoma de Madrid, Spain

15:30 – 15:45 **O.28 | Differential effects of diphenyl diselenide (PhSe)2 on mitochondria-related pathways depending on the cellular energy status in Bovine vascular endothelial cells**
Maria Monsalve

Instituto de Investigaciones Biomédicas Sols-Morreale, Spain

15:45 – 16:00 **O.29 | The role of NRF2 in the adverse effects of anticancer therapies: focus on cardio-oncology**
Vera Marisa Costa
Faculty of Pharmacy, University of Porto, Portugal

16:00 – 16:30 Coffee break

16:30 – 17:45 **Session 6: NRF2 and Metabolism**
Chairs: *Sofia Pereira, Portugal, and Tamara Saksida, Serbia*

16:30 – 16:45 **O.30 | NRF2 targeting in arterial hypertension associated with sleep apnea**
António B. Pimpão
iNOVA Medical School, UNL, Lisboa, Portugal

16:45 – 17:00 **O.31 | NRF2 regulates a neuronal fate by modification of mitochondrial metabolism, Ca2+ handling and permeability transition**
Andrey Y. Abramov
University College London, United Kingdom

17:00 – 17:15 **O.32 | Brain metabolic alterations promote faulty proteostasis and redox imbalance in Down syndrome neuropathology**
Fabio Di Domenico
Sapienza University of Rome, Italy

17:15 – 17:30 **O.33 | Identification of prognostic DNA methylation changes in NRF2 metabolic dysfunction associated steatotic liver disease**
Wim Vanden Berghe
University Antwerp, Belgium

17:30 – 17:45 **O.34 | Assessment of fructose consumption on blood-brain and testicular barriers, and NRF2 modulation: evaluation of hawthorn treatment**
Onur GökhanYildirim
Artvin Çoruh University, Turkey

17:45 – 18:00 **Concluding Remarks**
Chair: *Prof. Antonio Cuadrado, Spain*

20:00 **Gala Dinner**

Saturday, October 12

09:00 Lisbon walking Guided tour

Poster presentations

Nº	Presenter	Title
P.01	Antonija Tomić	Molecular modeling study of the structure and dynamics of the KEAP1 dimer and its complex with the Neh2 domain of NRF2
P.02	Bayram Yilmaz	Rotenone and Fam163a knockdown in the hypothalamus differentially regulate NRF2 levels, as well as other mitochondrial biogenesis and oxidative stress-related genes
P.03	Biljana Miova	Metformin upregulates critical antioxidant and protective genes in the NRF2 signaling pathway in streptozotocin-damaged INS-1 cells
P.04	Danushki Herath	Carbon monoxide counteracts pancreas dysfunction during obesity
P.05	Elena Rafailovska	Protective effects of mangiferin on streptozotocin-induced oxidative damage in INS-1 cells
P.06	Erkan Tuncay	Hyper K-acetylation-induced NRF2 inhibition causes contractile dysfunction in cardiomyocytes
P.07	Gülay Sezer	NRF-2 expression is involved in the concentration-dependent effects of boron on osteogenic differentiation of vascular smooth muscle cells
P.08	Joana Miranda	NRF2 induction attenuates MASLD in a stem cell-based hepatic *in vitro* model
P.9	Mafalda Pita	Laminin-α2 chain deficiency in skeletal muscle causes dysregulation of multiple cellular mechanisms
P.10	Margarida Pedro	Dimethyl fumarate: A repurposing strategy to treat age-related macular degeneration
P.11	Marisa Antunes	Current landscape of NRF2 clinical trials
P.12	Mihaela Matovina	RNAseq analysis of DPP3-KO 293FT cell line
P.13	Muhammet Karaman	Novel Schiff base derivatives as chemosensitizer candidate for chemotherapy cancer treatment: They impair the synthesis and recycling of GSH by inhibiting enzyme activity of G6PD modulated by NRF2
P.14	Nevena Savić	Sulforaphane prevents diabetes-induced hepatic ferroptosis by activating NRF2 signaling axis
P.15	Pelin Telkoparan-Akillilar	Exploring the IRE1-dependent miRNA regulation and NRF2 interaction in triple negative breast cancer
P.16	Rohini Srivastava	Target selectivity considerations for KEAP1 protein-protein interaction inhibitors – structure-activity relationships for KEAP1 and β-TrcP binding
P.17	Shuvajit Rakshit	Testing NRF2 activators in an age-related macular degeneration (AMD) mouse model
P.18	Sónia Pinho	Evaluating NRF2-activating compounds from the mediterranean diet for anti-inflammatory potential in obesity-related inflammation
P.19	Srđan Bjedov	Synthesis of bile acid derived NRF2 activators with functionalized steroidal rings
P.20	Tamara Saksida	The mechanism of action of HYCO-3, an NRF2 activator/CO releaser hybrid, in inhibiting type 1 diabetes development in a mouse model
P.21	Viktorija Maksimova	Potential of natural triterpenoid structures as a framework for design and development of perspective synthetic NRF2-modulating therapeutic agents

P.21 | Potential of natural triterpenoid structures as a framework for design and development of perspective synthetic NRF2-modulating therapeutic agents

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Since the discovery of NRF2, natural compounds like triterpene derivatives, taraxasterol, astragaloside, ursolic acid, and withaferin have been extensively studied, particularly because they were found to activate the NRF2 pathway as potent steroidal electrophiles [1]. These compounds are attracted to KEAP1, a nucleophilic protein, and by facilitating structural changes in KEAP1, lead to alterations in its shape and activation of NRF2.

Conversely, brusatol, a natural triterpene lactone, acts as an NRF2 inhibitor, suggesting its potential for sensitizing cancer cells, enhancing the effectiveness of cisplatin in a NRF2 dependent manner [2]. Its chemical structure served for further development of other semi-synthetic, halofuginone, that reduced NRF2 proteins level and induced selective cytotoxicity for NRF2 addicted cancer cell lines.

Oleanolic acid, a modest anti-inflammatory agent has been used as a basic structure for derivatization and obtaining of synthetic oleanane triterpenoids. Through a few modifications and the addition of Michaelis acceptors in the steroid rings bardoxolone (CDDO) was revealed as a potent NRF2 activator. Pre-clinical and clinical trials confirmed the ability to activate NRF2 pathway and act as anti-inflammatory, antineoplastic and reducing chemoresistance effects [1]. Another oleanone derivative, omaveloxolone, sparked interest in natural products with triterpene structures, following its FDA approval for Friedreich's ataxia treatment, last year [3].

Based on current research, natural triterpene compounds show significant potential for further development and optimization of semi-synthetic and synthetic therapeutic agents, offering a promising approach to targeting the NRF2 pathway.

References:

1. Zhang DD, Chapman E. The role of natural products in revealing NRF2 function. Nat Prod Rep. 2020 Jun 1;37(6):797-826.
2. Yu XQ, Shang XY, Huang XX, Yao GD, Song SJ. Brusatol: A potential anti-tumor quassinoid from Brucea javanica. Chin Herb Med. 2020 Aug 19;12(4):359-366.
3. Lee A. Omaveloxolone: First Approval. Drugs. 2023 Jun;83(8):725-729.