ANNOUNCEMENT

COST Action CA20121

BenBedPhar Training School 2023

NRF2 in noncommunicable diseases: from bench to bedside

Smolenice Castle, Slovakia
June 26—30, 2023

cost
EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

CENTRE OF EXPERIMENTAL MEDICINE
SLOVAK ACADEMY OF SCIENCES

INVITATION

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Dear BenBedPhar colleagues,

One of the most relevant COST tools is the implementation of training schools. Three training schools will be organized by BebBedPhar as part of our "capacity building objectives". The end goal is to promote a timely scientific community of NRF2 basic, pharmacological, and clinical researchers and entrepreneurs and to develop a "sense of belonging" to the EU scientific community. Our first training school is possible thanks to the positive and enthusiastic temper of Dr. Iveta Bernatova and the local organizers in Slovakia. They will make this training school a very successful vehicle for multidisciplinary training and international interaction of trainers and trainees.

Antonio Cuadrado

Chair of COST Action CA20121, BenBedPhar

INVITATION

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Dear trainers, dear trainees,

It is my great pleasure to invite you to the Training School of the COST CA20121 ***"Bench to Bedside Transition for Pharmacological Regulation of NRF2 in Noncommunicable Diseases (BenBedPhar)",*** *which will take place in the Congress Centre of the Slovak Academy of Sciences at Smolenice Castle in Slovakia. The Training School aims to provide comprehensive knowledge on the transcription factor NRF2 function which is a master regulator of multiple cytoprotective responses and a key molecular link among various noncommunicable diseases.*

During the Training School, distinguished scientists, the experts in NRF2 research, will present you with state-of-the-art knowledge on the role of NRF2 during aging, under stress, and in diseased states. They will also present the possibilities of pharmacological modulation of NRF2 function, tools for studying NRF2 as well as new perspectives of treatment of NRF2 associated disorders.

In addition, you will have the opportunity to present the results of your research. Discussions with experts and informal discussions of all participants will be an important part of the Training School that can help you accelerate your career growth.

Last but not least, an important benefit of this action is gaining new contacts, start networking and establishing personal friendships, which can significantly influence your further scientific interests.

I believe that the picturesque premises of the Congress Centre of Smolenice Castle and its surroundings will contribute to a good working atmosphere and positive mood during your stay.

We look forward to seeing you in Smolenice Castle.

On behalf of the local organizers

Iveta Bernatova

LOCAL ORGANIZERS

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Iveta Bernátová, head of the Local Organizing Committee (Action Management Committee member), senior researcher, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

Miroslava Kvandová, post-doc, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

Peter Bališ, researcher, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

Michal Kluknavský, post-doc, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

Andrea Mičurová, PhD. Student, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

VENUE

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Smolenice Castle

Congress Centre of the Slovak Academy of Sciences, Zamocka 18, Smolenice, Slovakia

Information

kcsmolenice.sav.sk/en/

TRAVEL INFORMATION

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

From the M.R. Štefánik Airport, Bratislava, Slovakia

After arrival take public buses or a taxi to the central Bus Station Nivy (also called Central bus station, Autobusová stanica Nivy or Stanica Mlynske Nivy) which are located in front of the exit door. The journey by public transport can take around 45 minutes, depending on the traffic situation. By taxi, Bolt or Uber it takes about 15 minutes.

From the Vienna/Schwechat Airport, Austria

Take a shuttle bus directly to Bratislava central Bus Station Nivy. Bus stops are located in front of doors of Vienna/Schwechat Airport. The journey takes around 60 minutes and buses depart from the airport approximately each 30 minutes. One way ticket costs 5 -15€, depending on provider. You can use Slovak Lines, Flixbus, or Regio jet. Tickets are available online on omnio.com, flixbus.com, slovaklines.sk/en/ or regiojet.com/ or directly in the bus.

From Bratislava to Smolenice Castle and back

Participants will meet at the pre-announced Meeting point at the Bus Station Nivy on June 26, 2023 between 1:00 p.m. and 2:00 p.m. The Bus Station is located in the underground of the Nivy shopping centre. More information is available at nivy.com/en/buses and bratislava-slovakia.eu/places/central-bus-station .

The Nivy Mall offers a wide range of services for travel, dining and shopping. There is a free green park on the roof. A bus to Smolenice Castle will be provided for the participants from the Bus Station Nivy. On the return trip, the bus will depart from Smolenice Castle on June 30, 2023 at 2:00 p.m. to Bratislava, Bus Station Nivy. The journey from Bratislava to Smolenice takes approximately one hour.

Other ways to get to Smolenice Castle

More information about train, bus, taxi or car transport to the Castle can be found at kcsmolenice.sav.sk/en/travel-information/ website. The Castle provides free parking for participants in the area of the Castle or nearby parking lot at the hill. Entry to the Castle hill is permitted for congress participants.

REGISTRATION

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Registration

The Training School has a capacity for 40 trainees of which BenBedPhar will defray registration, the cost of travel and allowance (which will cover accommodation, catering and short-distance travel) for 21 trainees. The selection of trainees will be made among the PhD. students and young researchers participating in BenBedPhar project, considering quality of the submitted abstract and gender and geographical balance.

Trainees participating on their own will cover **registration fee 100 €,** travel expenses and all other expenses listed below by themselves.

We kindly ask all trainees to register via the Registration form which will be available online on https://form.jotform.com/230333681518050 or using this QR code with the password that will be announced to participants whose abstracts have been accepted for presentation.

Registration will be open from **March 15, 2023** to **April 15, 2023**.

Cancelation of participation

If you have to cancel your participation, please, inform the local organizers as soon as possible by email to Iveta.Bernatova@savba.sk. The registration fee will be returned, with a reduction necessary for the bank fees, if cancelation is made **before June 15, 2023.**

ABSTRACTS SUBMISSION

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Please, submit the abstract and short description of your CV and research interests by email to Michal.Kluknavsky@savba.sk and Iveta.Bernatova@savba.sk

Deadline for abstract submission is **March 10, 2023**
Decision will be announced by **March 15, 2023**

The Abstract form is at the end of this Announcement. The length of the CV and abstract sections may vary, but please do not exceed the maximum length of one page.

ACCOMODATION AND CATERING

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Accommodation

The Castle provides accommodation mainly in shared double rooms. For that reason, the organisers will accommodate you together with another Training School participant. Accommodation will be pre-booked for all participants by the local organizers based on the preference indicated in the Registration form. Price includes breakfast. Free wifi is available in the Castle, smoking and pets are not allowed.

Double room	99 €/night
Double room shared	49.5 €/night/person
Triple room shared	41 €/night/person

Catering

During the coffee breaks, free coffee/tea/water and light refreshment will be served. Otherwise, meals will be served in the Lunch room in the Castle. Due to the Castle location, meals will be pre-ordered for you by the local organisers. The first meal served will be Welcome dinner on June 26, 2023. Last meal served will be lunch on June 30, 2023. Full boarding consist of welcome dinner, four lunches, two dinners and farewell BBQ. Expected price for catering is around **140 €.** Please, specify your accommodation and meal preferences in the Registration form. Accommodation and meals will be paid by all participants directly in the Castle Reception. Main credit/debit cards as well as cash are accepted.

Accommodation and catering for COST-supported participants will be reimbursed in the form of a daily allowance.

ACADEMIC PROGRAMME

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Academic programme includes 50- and 20-min lectures of invited experts in NRF2 research, 15-min oral presentations of selected participants and moderated posters. **All participants are asked to present oral presentation or poster.** Oral presentations will be selected by invited experts on the basis of Abstracts.

All presentations include 5-minute-long discussion. Posters should be assembled on June 27, 2023 before 11:00 and discarded after the last poster session. Poster sessions will be moderated. Each author is expected to provide a brief (~5 min) information on the main findings of his/her study.

In addition, academic discussions with experts are included in programme and informal meetings may take place throughout the duration of the Training School.

All participants will receive a certificate of participation.

PROGRAMME OVERVIEW

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Central European Time	Monday June 26, 2023	Tuesday June 27, 2023	Wednesday June 28, 2023	Thursday June 29, 2023	Friday June 30, 2023
8:00-9:00		Breakfast	Breakfast	Breakfast	
9:00 -09:25		**NRF2 in inflammation** A. Dinkova-Kostova	**NRF2 and cardio-vascular diseases** A. Grochot-Przeczek	**NRF2 in liver diseases** A. Cuadrado	Breakfast and check-out
9:25-9:50				**NRF2 in neurologic diseases** M.G. López	**NRF2 pharmacology** A. Dinkova-Kostova
9:50 -10:15		**NRF2 in ageing** I. Trougakos	**NRF2 in neuro-degenerative diseases** M. G. López	**NRF2 in radiation therapy and cancer** G. Manda	**Tools to study NRF2** A. Grochot-Przeczek
10:15-10:40	**14:00 Departure from Bratislava to Smolenice Castle**			**NRF2 in non-mammalian species** I. Trougakos	10:15-10:45 **2 Student oral presentations**
10:40-11:15		Coffee break	Coffee break	Coffee break	Coffee break
11:15-12:05		**NRF2 in stress responses** I. Bernatova	**6 Student oral presentations and discussions**	**Poster viewing and discussions**	11:15-12:15 **4 Student oral presentations**
12:05 -12:55		**NRF2 biomarkers in blood** G. Manda			12: 15 **Concluding remarks** A. Cuadrado
12:55 -14:00		Lunch break	Lunch break	Lunch break	Lunch break
14:00-16:00		**Poster viewing and discussions**	**Social programme Hiking - Cave Driny visit**	**Social programme Excursion to Red Stone Castle**	**14:00 Departure from Smolenice Castle to Bratislava**
16:00-16:30	**Registration and accommodation**	Coffee break			
16:30-17:00		Meet the Experts - Students discussion E1+2			
17:00-17:30	**Opening and General introduc-tion to NRF2** A. Cuadrado	Meet the Experts - Students discussion E3+4			
17:30-18:00		Meet the Experts - Students discussion E5+6+7			
18:00-18:30	**Social programme Smolenice Castle Tour**		**Practical Presentations** I. Bernatova		
18:30-19:00		Student mixer			
19:00-19:30	Break	Break	Break	Break	
19:30-21:30	**Welcome diner**	**Dinner**	**Dinner**	**Farewell BBQ**	

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

ANTONIO CUADRADO

Department of Biochemistry, Medical College, Autonomous University of Madrid, Madrid, Spain. E-mail: antonio.cuadrado@uam.es

Prof. Antonio Cuadrado is a full professor of Biochemistry and Molecular Biology at the Department of Biochemistry, Medical School, Autonomous University of Madrid. He obtained his PhD degree in Biology in 1985 and enjoyed several postdoctoral stays in the National Cancer Institute -NIH with the help of Fulbright and Fogarty fellowships. He established his independent laboratory as Professor of Biochemistry in 1997 with a main interest on the study of molecular mechanisms involved in initiation and progression of chronic diseases. For the past years his main lane of research has been the validation of transcription factor NRF2, master regulator of cellular homeostasis as a new therapeutic target in chronic diseases with particular emphasis in neurodegenerative diseases (Alzheimer and Parkinson) and in fatty liver diseases. His current interest is the development of new NRF2-modulating drugs. Dr. Cuadrado has published over 160 primary and review articles, of which more than 80 are related to the role of NRF2 in physiological and pathological responses to disease.

Presentaton I: General introduction to NRF2

Transcription factor Nrf2 (Nuclear factor (erythroid-derived 2)-like 2) is a master regulator of cellular homeostasis that controls the expression of more than 1% of human genes related to biotransformation reactions, redox homeostasis, energy metabolism, DNA repair, and proteostasis. These genes possess a cis-acting regulatory sequence termed antioxidant response element (ARE). Structurally, it is a member of the cap 'n' collar (CNC) subfamily of basic region leucine zipper (bZip) transcription factors and makes heterodimers with other bZip proteins, of which small MAFs G, K and F are the best characterized. Its activity has a tremendous impact on physiology and pathology and therefore it is very tightly regulated by a complex array of transcriptional regulators and post-

translational modifications, that ensure proper transcriptional activity under basal conditions and under adaptation to environmental changes. The main mechanism of regulation of NRF2 is at the level of protein stability. Most studies have focused on the role of the electrophile and redox sensor Kelch-like ECH-associated protein 1 (KEAP1) to adjust NRF2 protein levels to metabolic demands. KEAP1 interacts with two regions of NRF2 (amino-acid sequences DLG and ETGE) located at the Neh2 N-terminal domain to direct ubiquitination by the Cullin-3/Rbx1 complex and proteasome degradation of NRF2. On electrophilic modification or oxidation of KEAP1, the interaction with NRF2 is disrupted. Then, NRF2 escapes degradation and targets ARE genes to increase the capacity of antioxidant and biotransformation reactions. In addition to the very well established regulation by the ubiquitin E3 ligase adapter KEAP1, another mechanism of NRF2 regulation is based on signaling pathways that regulate glycogen synthase kinse-3(GSK-3).This kinase phosphorylates specific serine residues in the Neh6 domain of NRF2 to create a degradation domain that is then recognized by the ubiquitin ligase adapter β-TrCP and tagged for proteasome degradation by a Cullin1/Rbx1 complex. Several electrophilic compounds induce NRF2 due to sulfhydryl modification of specific redox sensitive cysteines in redox sensor proteins such as KEAP1 and PTEN and thus impact on NRF2 stability by either of these two mechanisms. Many of these compounds have been used as nutraceuticals and some of them have reached clinical evidence. The most successful case so far reported is the ester derivative of fumaric acid, dimethyl fumarate (DMF). DMF crosses the gastrointestinal barrier where it is converted into monomethyl fumarate (MMF). Some very potent synthetic triterpenoids have been studied in teh context of diabetic nephropathy (bardoxolone methyl) or Friedreich ataxia (omaveloxone). Another NRF2 inducer that has reached the level of clinical studies is the isothiocyanate sulforaphane (SFN) isolated from broccoli sprout extracts. Considering that Nrf2 elicits a defense against multiple stress conditions, it has shown its negative side in some concers where somatic mutations lead to it constitutive activations. New strategies are being developed to inhibit NRF2 under these conditions. We will discuss along this course the mechanistic regulation of NRF2 and its impact in physiology and pathology.

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Presentation II: NRF2 in liver diseases

Around 23-25% of adults worldwide have Non-alcoholic fatty liver disease (NAFLD) and among them 20% develop non-alcoholic steatohepatitis (NASH), which, together with its comorbidities, is one of the main causes of mortality. At this time, there is not a drug specifically approved for the treatment of NASH, which probably reflects that NASH is a clinical manifestation that gathers several pathomechanisms. In fact, NASH is characterized by the presence of oxidative stress, inflammation, and metabolic alterations. These three crucial hallmarks can be targeted with a single hit by activating the transcription factor Nuclear factor erythroid 2 Related Factor 2 (NRF2). In this lecture, we will review the mechanisms that point NRF2 as a promising target to endorse a disease modifying therapy for NASH and fibrosis. Three E3 ubiquitin ligases appear to control NRF2 protein levels in liver: Kelch-like ECH-associated protein 1 (KEAP1), β-transducin repeat-containing protein (β-TrCP), and HMG-CoA reductase degradation protein 1 (Hrd1, also called synoviolin (SYVN1)). Many processes that downregulate NRF2 are triggered by transforming growth factor-beta (TGF-β), with oxidative stress amplifying its signaling. In animal models, knockout of NRF2 increases susceptibility to NASH, while pharmacological activation of NRF2 by inducing agents that target KEAP1 or beta-TrCP prevent NASH development, or if NASH has been initiated, suppresses liver steatosis and progression towards fibrosis. There is therefore compelling evidence that pharmacological activation of NRF2 may be a comprehensive strategy to treat NASH and fibrosis.

INVITED TRAINERS

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

GINA MANDA

Radiobiology Laboratory, Victor Babes National Institute of Pathology, Bucharest, Romania, Email: gina.manda@ivb.ro

Prof. Gina Manda is a senior scientist, Head of the Radiobiology Department at "Victor Babeș" National Institute of Pathology, Bucharest, Romania. She has an H-index of 20 with 148 ISI-indexed papers and more than 1800 citations. She is the Vice-leader of the COST Action CA20121 BenBedPhar. She studied Physics at the University of Bucharest (1985) and holds a Ph.D. in Biophysics (1996). Her actual research is focused on redox biology and immunology in pathology (neurodegeneration), radiobiology (radiotoxicology) and cancer therapy (new radiotherapeutic approaches and photodynamic therapy). Through collaboration with the European Space Agency, she is testing NRF2 therapeutics for protection against the deleterious effects of galactic cosmic rays on astronauts. In addition, she is a member of the BIOSPHERE consortium focused on the synergic cellular action of terrestrial secondary cosmic rays and UV radiation.

Presentation I: NRF2 biomarkers in blood

Low-grade oxidative stress and inflammation seem to precede the onset of overt symptoms in most of chronic noncommunicable diseases due to the deregulation the NRF2 signaling pathway at local and systemic level. Recent clinical evidence of NRF2 disturbance in chronic diseases will be summarized. The relevance of NRF2 as cellular or soluble biomarker in blood will be discussed as a non-invasive approach for monitoring disease since its early stages or NRF2-targeted therapeutic strategies addressing both redox disturbances and inflammation. Transcriptomic data on the NRF2 molecular fingerprint in the blood of patients with Alzheimer's disease versus age-matched controls will be discussed.

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Presentation II: NRF2 biomarkers in blood

Low-grade oxidative stress and inflammation seem to precede the onset of overt symptoms in most of chronic noncommunicable diseases due to the deregulation the NRF2 signaling pathway at local and systemic level. Recent clinical evidence of NRF2 disturbance in chronic diseases will be summarized. The relevance of NRF2 as cellular or soluble biomarker in blood will be discussed as a non-invasive approach for monitoring disease since its early stages or NRF2-targeted therapeutic strategies addressing both redox disturbances and inflammation. Transcriptomic data on the NRF2 molecular fingerprint in the blood of patients with Alzheimer's disease versus age-matched controls will be discussed.

INVITED TRAINERS

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

ALBENA T. DINKOVA-KOSTOVA

Division of Cellular and Systems Medicine, University of Dundee School of Medicine, United Kingdom, Email: a.dinkovakostova@dundee.ac.uk

Prof. Albena T. Dinkova-Kostova is a Professor of Chemical Biology at the University of Dundee School of Medicine (UK). She graduated in Biochemistry and Microbiology from Sofia University (Bulgaria) and obtained her PhD degree in Biochemistry and Biophysics from Washington State University (USA). She subsequently trained in Pharmacology at Johns Hopkins University School of Medicine (USA), where she continues to hold an Adjunct Professor position. She joined the University of Dundee in 2007 as a Research Councils UK Academic Fellow and a research group leader. Her group collaborates with basic scientists and clinicians, and with the pharmaceutical industry. In her research, at the interface of Chemical Biology and Medicine, she is committed to understanding how cells and organisms respond to oxidative, inflammatory, and metabolic stress, and is working towards development of strategies for protection against chronic disease. She was named among the top influential academics in Clarivate's Highly Cited Researchers 2019, 2020, 2021 and 2022 lists.

Presentation I: NRF2 in inflammation

The transcription factor nuclear factor erythroid 2 p45-related factor 2 (NRF2; encoded by *NFE2L2*) and its principal negative regulator, Kelch-like ECH associated protein 1 (KEAP1), control the expression of large networks of genes encoding cytoprotective proteins that provide adaptation to oxidative, electrophilic, inflammatory, and metabolic stress. The role of NRF2 in drug metabolism has been known since the discovery of the transcription factor in the 1990s. A decade later, a structure-activity study of a large series of synthetic triterpenoid analogues of oleanolic acid, which were originally developed as inhibitors of cellular inflammatory processes, revealed a linear correlation spanning 6 orders of magnitude of concentration between the anti-inflammatory andcompounds representing seven chemically distinct classes of NRF2 activators identified VNRF2-activating activities of these compounds. A follow-up study of structurally-diverse compounds representing seven chemically distinct classes of NRF2 activators

identified suppression of inflammation as a consistent property of NRF2 activators. This correlation suggested that the two activities of these compounds are mechanistically linked. Subsequent experiments in NRF2-deficient murine macrophages demonstrated that the anti-inflammatory activity of such compounds is partly dependent on NRF2. In addition to xenobiotics, NRF2 is also activated by endogenous metabolites, such as the cis-aconitate-derived itaconate, which accumulates to millimolar concentrations in inflammatory macrophages, and has a crucial role for the resolution of inflammation. Most recently, high-resolution quantitative proteomics showed that NRF2 is a critical factor governing redox and intermediary metabolism and facilitating mitochondrial adaptation in macrophages encountering pro-inflammatory stimuli. This presentation will provide an overview of the anti-inflammatory role of NRF2 activation in a number of experimental systems, including primary murine macrophages, animal models, and peripheral blood mononuclear cells (PBMCs) and skin of human subjects.

Presentation II: NRF2 pharmacology

Inducible transcription factor nuclear factor erythroid 2 p45-related factor 2 (NRF2; encoded by *NFE2L2*) is a member of the human cap'n'collar (CNC) basic-region leucine zipper transcription factor family. The protein products of its target genes perform versatile cytoprotective functions, including antioxidant, anti-inflammatory, metabolic and drug-metabolizing, and have roles in the maintenance of protein homeostasis. Through its transcriptional targets, NRF2 activation orchestrates a comprehensive and long-lasting protection that allows adaptation and survival under diverse forms of cellular and organismal stress. Pharmacologic NRF2 activators have shown protective effects in numerous models of human disease and benefits in human intervention trials, and NRF2 is an attractive therapeutic target, with several NRF2 activators in various stages of drug development, and one compound, dimethyl fumarate, in clinical practice for the treatment of remitting-relapsing multiple sclerosis and psoriasis. The advances in drug development of NRF2 modulators are however accompanied by numerous challenges, including target specificity, monitoring target engagement/pharmacodynamic responses, short/long-term safety considerations, identifying the most appropriate disease indications, and understanding the extent and implications of variation in NRF2 activity. This presentation will outline the rationale for targeting NRF2, and the recent advances and challenges in drug development of NRF2 activators.

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

ANNA GROCHOT-PRZĘCZEK

Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland, Email: anna.grochot-przeczek@uj.edu.pl

Anna Grochot-Przeczek is an associate professor in the Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics, and Biotechnology, Jagiellonian University in Krakow, Poland. She studies the molecular mechanisms that regulate the function of endothelial cells and blood vessels with a focus on NRF2/KEAP1 pathway, ageing and S-nitrosation. Currently, she investigates the importance of NRF2/KEAP1 imbalance and loss of proteostasis in the function of blood vessels.

Presentation I: NRF2 and cardiovascular diseases

Cardiovascular diseases (CVDs), a group of disorders of the heart and blood vessels, are the leading cause of death worldwide. Many of them are associated with impairment of the defence mechanisms against oxidative stress. Therefore, NRF2 being a master orchestrator of cellular stress response is an interesting subject of cardiovascular research. In the talk, I will give an overview of the mechanisms related to the role of NRF2 in cardiovascular diseases, such as atherosclerosis, heart failure, and abdominal aortic aneurysm.

Presentation II: Tools to study NRF2

Using the right tools is a key for a precise understanding of the molecular mechanisms that determine physiological and pathological conditions. In the field of NRF2 we have many tools which help us investigate its importance in various experimental settings. However, it is critical to know several subtle details that may affect data interpretation. In the talk, I will present several misconceptions that linger in the literature.

INVITED TRAINERS

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

MANUELA G. LOPEZ

Department of Pharmacology, Medical School and Institute Teofilo Hernando. Autonomous University of Madrid, Spain, Email: manuela.garcia@uam.es

Prof. Manuela G. Lopez is MD PhD and full professor of Pharmacology at the Department of Pharmacology in the School of Medicine, Universidad Autónoma de Madrid (UAM), Spain. Currently, she heads the Institute Teofilo Hernando for drug discovery (http://www.ifth.es/) that belongs to UAM. Her group, "NeuroprotectionLab" (http://neurodiscovery-ndd.com/gt1), has particular interest in the identification of new potential therapeutic targets to develop innovative and disease modifying therapies for neurodegenerative diseases, with special focus in modulating neuroinflammation (microglia-astrocyte interaction), oxidative stress and autophagy. Within the field of NRF2, she has contributed to the understanding of NRF2 in pain, depression, stroke and neurodegenerative diseases, together with the development of different NRF2 multitarget drugs in collaboration with medicinal chemists. Currently, she is coordinating a drug development project to identify Keap1-NRF2 inhibitors with potential use in Alzheimer's disease (AD).

Presentation I: NRF2 in neurodegenerative diseases

In this presentation we will go through the evidence from preclinical to clinical studies that indicate that NRF2 is dysfunctional in different neurodegenerative diseases. Studies from NRF2 knockout mice have been very helpful to determine how this transcription factor can impact in Alzheimer´s disease pathology. Once shown the proof of concept that induction of NRF2 could be an innovative strategy to develop drugs to achieve a disease modifying effect for AD and other related dementias, we will present the student an example to understand the drug development process for an NRF2 inducer for AD.

Presentation II: Implication of NRF2 in Depression

In this lecture, we will review the major hypotheses on the physiopathology of depression. Current treatments for depression are based mainly on the monoaminergic or serotoninergic dysfunction hypotheses; however, the response rates of these drugs are limited (around 50 % after 4 weeks treatment). Focusing in the more recent inflammatory hypothesis and data from NRF2 knockout animals, we will envision that NRF2 induction may be an interesting alternative to develop new drugs with a totally novel mechanism of action for depression. We will present preclinical data that will support this hypothesis, including the effects on an endogenous NRF2 compound-agmatine. Finally, we will present evidence obtained from patients with major depression.

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

IOANNIS TROUGAKOS

Department of Cell Biology and Biophysics, Faculty of Biology, National and Kapodistrian University of Athens, Athens, 15784, Greece

Email: itrougakos@biol.uoa.gr; http://scholar.uoa.gr/itrougakos/home

Ioannis Trougakos obtained his Ph.D. in Cellular-Developmental Biology from the National and Kapodistrian University of Athens (NKUA), Greece. He has worked as Research Scientist at EMBL, Germany, CBM "Severo Ochoa", Spain and at NHRF, Athens, Greece; he was also research visitor at EMBL and at the Netherlands Cancer Institute. Dr. Trougakos was elected Research Lecturer at NHRF and currently he serves as Professor and Director of the "Cell Biology" lab at the Faculty of Biology, NKUA. Dr. Trougakos has published articles (>190) in high-ranking journals, chapters in international books and he co-authored an academic book (citations ~19500; h-Index = 45 / i10-index = 129); he is also co-inventor in several patents. His group is funded by private (GR, EU, USA) and public (GR, EU) entities; also, the group participates in contractual activities with the Industry.

Presentation I: NRF2 in ageing

Aging is a complex phenomenon caused by the time-dependent loss of cellular homeodynamics and consequently of physiological organismal functions. This process is affected by both genetic and environmental (e.g., diet) factors, as well as by their constant interaction. The balanced functionality of (among others) cellular antioxidant and proteostatic modules is central to genome, proteome and mitochondrial stability. The antioxidant response system comprising (among others) the ubiquitously expressed NFE2 -related transcription factor 2 (NRF2) and its redox-sensitive cytoplasmic inhibitor Kelch-like ECH-associated protein 1 (KEAP1) defends tissues against oxidative stress, thereby protecting against pathologies that relate to DNA, protein, and/or lipid oxidative damage. These NRF2 functions, along with the extensive functional wiring of genomic,

proteostatic and mitostatic modules, become less efficient in higher metazoans during advanced age. The gradual dysfunction of the NRF2/KEAP1 regulatory network during aging is (among others) a driving force for most age-related diseases.

Presentation II: NRF2 in non-mammalian species

A central module of antioxidant defenses in higher metazoans refers to the ubiquitously expressed NFE2-related transcription factor 2 (NRF2), which along with its redox-sensitive cytoplasmic inhibitor Kelch-like ECH-associated protein 1 (KEAP1), defends tissues against unbalanced oxidative load, providing thus protection against oxidative damage of biomolecules. The NRF2-KEAP1 system is seemingly evolutionarily conserved in different organisms of the animal kingdom and studies in lower animals and model organisms (e.g., zebrafish, *Drosophila melanogaster* and *Caenorhabditis elegans*), including recent advances in genome projects, have provided important information regarding the evolvement of these anti-stress machineries during evolution. We will discuss the NRF2-KEAP1 system in non-mammalian model animals, providing also input on the evolutionary history of this ancient cell defense system.

INVITED TRAINERS

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

IVETA BERNATOVA

Department of Experimental Hypertension, Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

Iveta.Bernatova@savba.sk

Iveta Bernatova is a senior scientist, Head of the Department of Experimental Hypertension Centre of Experimental Medicine, v.v.i., Slovak Academy of Sciences, Bratislava, Slovakia. She studied Biochemistry, holds a Ph.D. degree in Chemistry and scientific degree Doctor of Science (D.Sc., an equivalent of research professor) in Animal Physiology. She completed postdoctoral stay at the School of Medicine, Wright State University, Dayton, Ohio in Physiology and Pharmacology. Her research is focused on integrative physiology, mainly on the mechanisms of blood pressure regulation in various experimental models. Currently she is focused on the role of NRF2 in chronic social stress-induced alteration in the heart and livers with focus on iron metabolism.

Presentation I: NRF2 in stress responses

Chronic stress is considered a risk factor associated with the development of various non-communicable diseases. Activation of stress systems leads to a cascade of neuroendocrine, cardiovascular, behavioral, metabolic and immune responses to ensure the integrity and survival of the organism. Yet, long-lasting and/or intensive stressors can lead to diseased states, in which oxidative stress and inflammation are present. NRF2, among others, is involved in the regulation of various metabolic pathways such as glucose metabolism, fatty acid synthesis, iron and heme metabolism as well as glutathione synthesis and utilization. This lecture will focus on systemic and molecular mechanisms in stress that are regulated by NRF2.

Practical presentation

The aim of this session is to show the participants selected alternative laboratory methods that are in line with the 3R (Replacement, Reduction and Refinement) principle in animal experimentation. Participants will see the alternative methods of testing the effects of various substances without the use of laboratory animals. This section will be organised in collaboration with Dr. Helena Kandárová, who is WG5 leader in COST action 21108 European Network for Skin Engineering and Modeling (NETSKINMODELS).

SOCIAL PROGRAMME

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Smolenice Castle Tour. The origin of Smolenice Castle dates back to the 13th century. Castle went through periods of glory but also of complete ruins. It was renovated after World War II and since 1953 it has been the property of the Slovak Academy of Science. We will learn about its history and premises in a short tour after arrival. This tour is free for all participants.



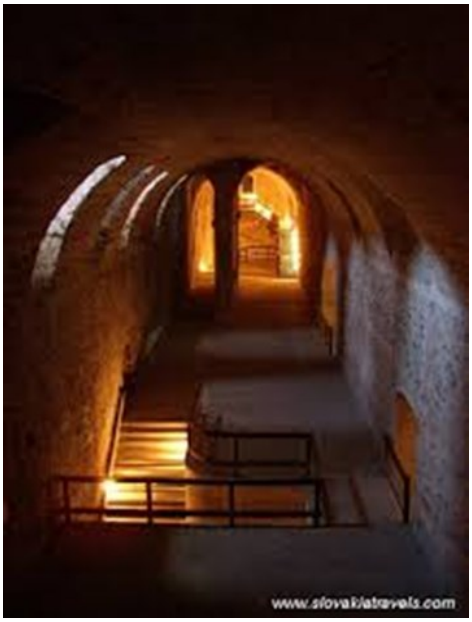
Hiking to Cave Driny. Smolenice Castle is surrounded by the forests of the Small Carpathians and there are many hiking trails, historical places and natural attractions in its vicinity. Only about 4 km walk from the Smolenice Castle is located a charming underground world full of peculiar stalactites and small ponds — Cave Driny. We will make a hiking afternoon and visit this cave. Temperature in the cave is 7 °C. Therefore, bring suitable shoes and clothes. The entrance fee is around 10€. All participants will pay the entrances fee by themselves.


Cave Driny: lenght 450 m, temperature ~7 °C, time of visit ~35 min

SOCIAL PROGRAMME

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

Red Stone Castle Tour. The first mention of the Red Stone Castle was in the first half of the 13th century. Castle is known for its huge cellars. The Red castle cellars were built between 1538 and 1555. They have six floors. These cellars are among the largest in Europe. After World War II, it became a museum. Complete entrance fee is about 15€ (deductions are available for holders of ISIC, ITIC and EURO<26 cards) and expected bus transportation is around 15€/person. More information is at https://hradcervenykamen.sk/?lang=en , https://www.slovakia.com/castles/cerveny-kamen/.
All participants will pay the entrances fee and transportation by themselves.



Recommended Abstract Form

First Name, Surname

Affiliation:

Position:

Email:

Short description of your CV and research interests.

Recommended font: Century Gotic 12, Line space: 1

Title of the presentation

Background: Century Gotic 12, Line space: 1
Methods:
Results:
Conclusions:

ACKNOWLEDGEMENTS

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases: from bench to bedside

This Training School is supported by COST Action 20121

Bench to Bedside Transition for Pharmacological Regulation of NRF2 in Noncommunicable Diseases (BenBedPhar)

cost
EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

CENTRE OF EXPERIMENTAL MEDICINE
SLOVAK ACADEMY OF SCIENCES