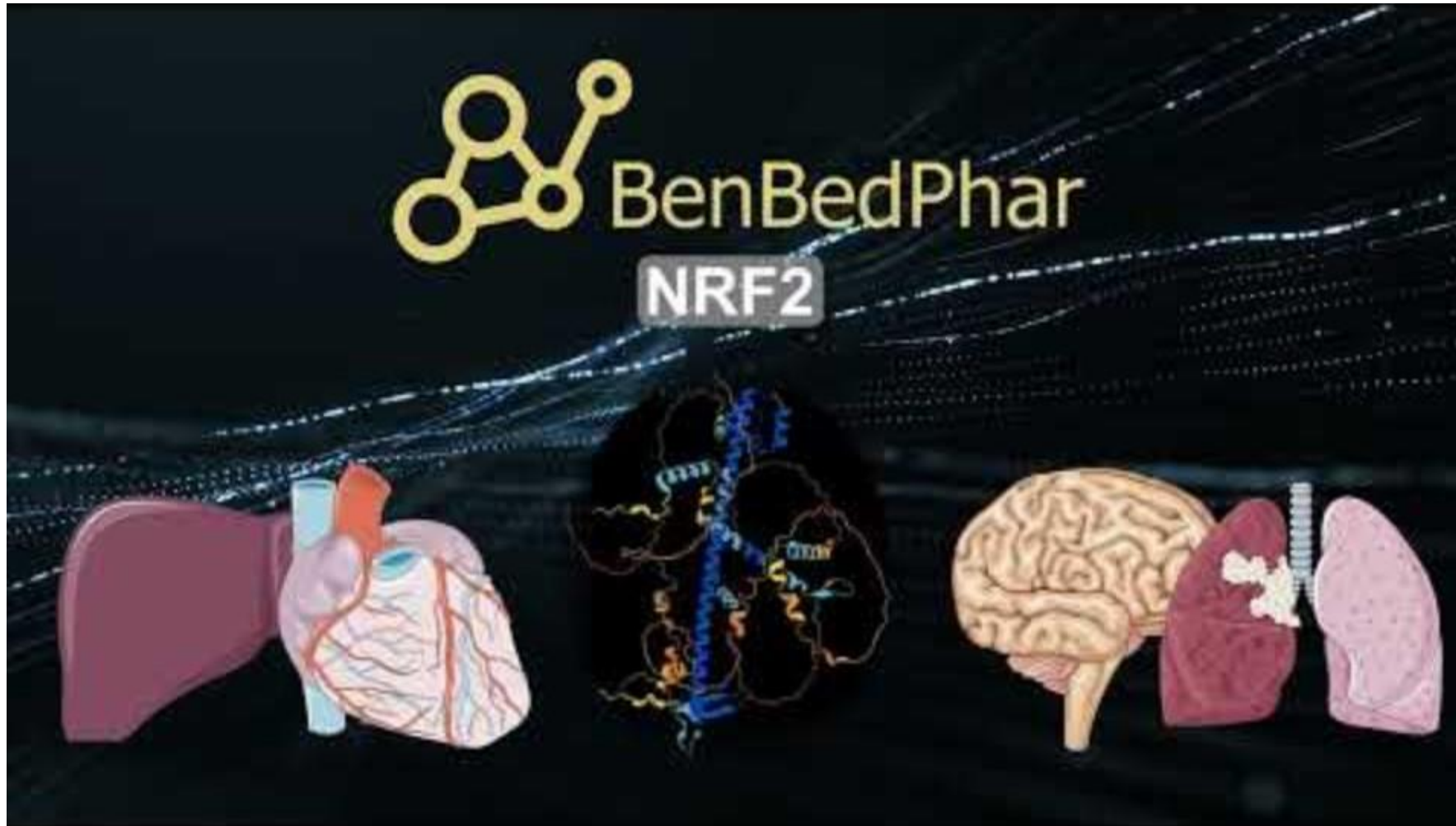


**Bench to Bedside transition
for Pharmacological regulation of NRF2
in non communicable diseases
BenBedPhar**

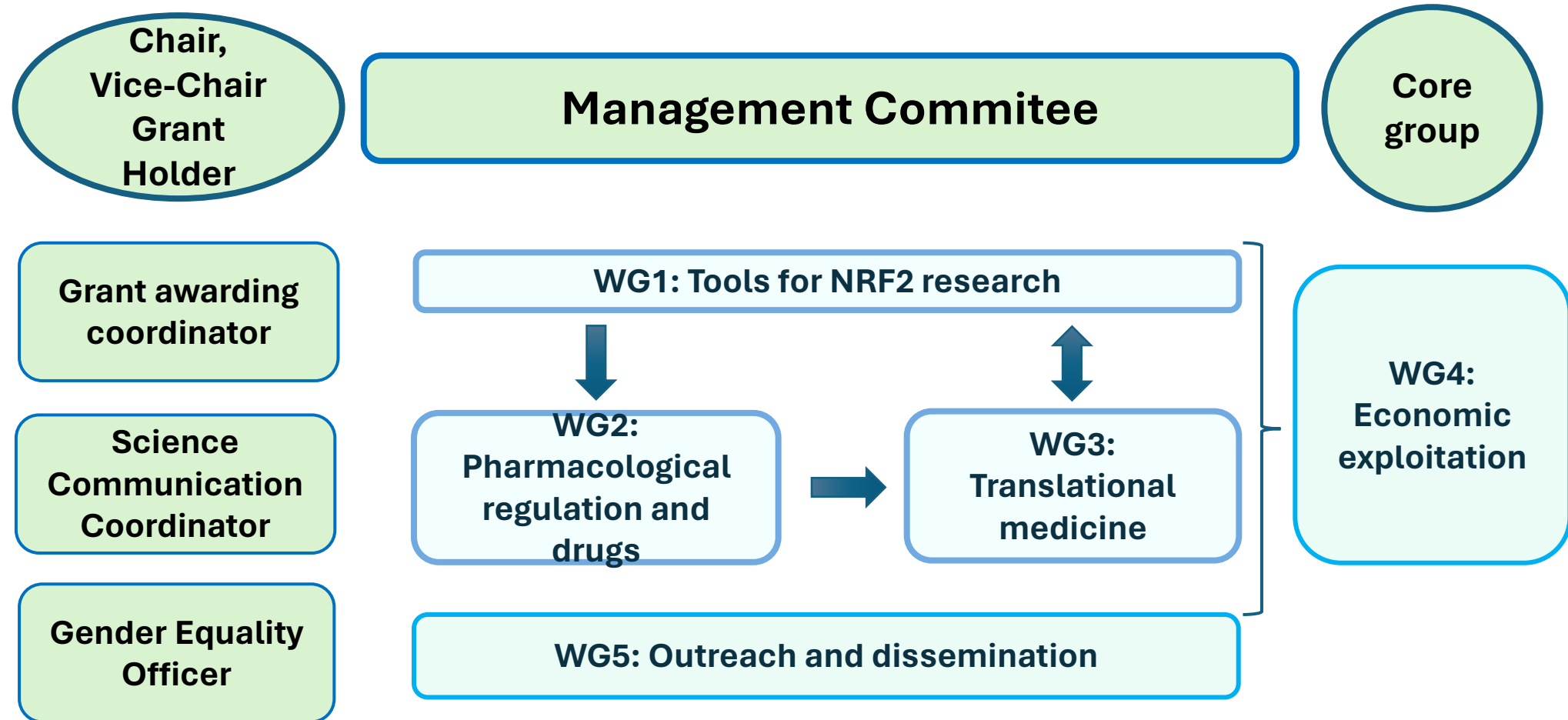
COST Action CA20121

To translate **NRF2-related research** into the stream of EU social, clinical and economic sectors, providing **innovative therapeutics** for some Non-communicable diseases

BenBedPhar Challenge



BenBedPhar structure



Chair

Antonio Cuadrado

Department of Biochemistry, Medical College,
Autonomous University of Madrid,
Madrid, Spain.

E-mail: antonio.cuadrado@uam.es



Vicechair

Gina Manda

Radiobiology Laboratory,
Victor Babes National Institute of Pathology,
Bucharest, Romania

Email: gina.manda@ivb.ro



Current WG leaders and co-leaders

WG1: Tools for NRF2 research

leader: Anna Grochot-Przeczek (**Poland**)

co-leader: George Spyrou (**Cyprus**)

WG2: Pharmacological regulation and drugs

leader: Albena Dinkova-Kostova (**UK**)

co-leader: Ana I. Rojo (**Spain**)

WG3: Translational medicine

leader: Cristina Mongerster (**Austria**)

co-leader: Brigitte Winklhofer-Roob (**Austria**)

WG4: Economic Exploitation

leader: Santiago Cuevas (**Spain**)

co-leader: Ioannis Trougakos (**Greece**)

WG5: Outreach and dissemination

leader: Brigitta Buttari (**Italy**)

co-leader: Ana Rita Carlos (**Portugal**)z

Other current leadership positions:

Grant Awarding Committee:

Irina Milisav (**Slovenia**)

Andreas Daiber (**Germany**)

Torstern Born (**Luxemburg**)

Gender Equality Officer:

Silvai Giordani (**Ireland**)

International Advisors:

Masayuki Yamamoto (**Japan**)

Hozumi Motohashi (**Japan**)

Tomas Kensler (**USA**)

Donna Zhang (**USA**)

Gina DeNicola (**USA**)

Science Communication Coordinator:

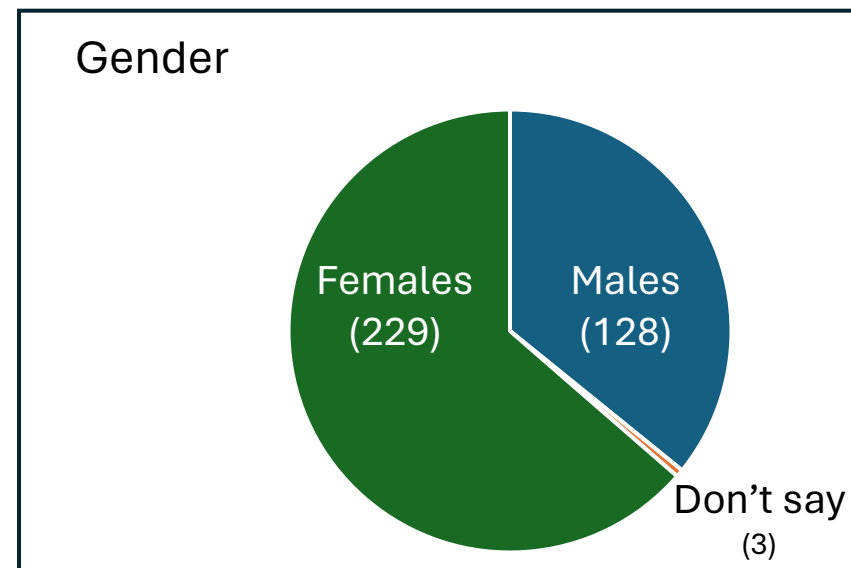
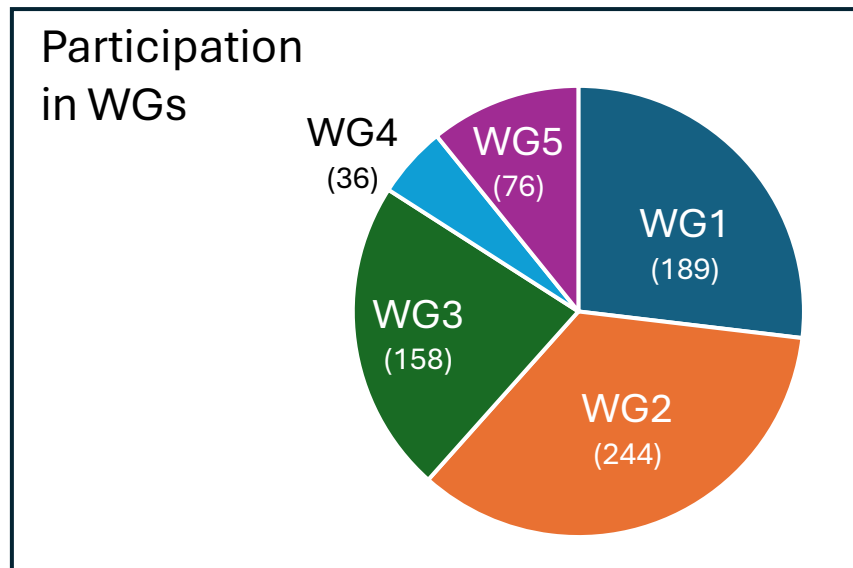
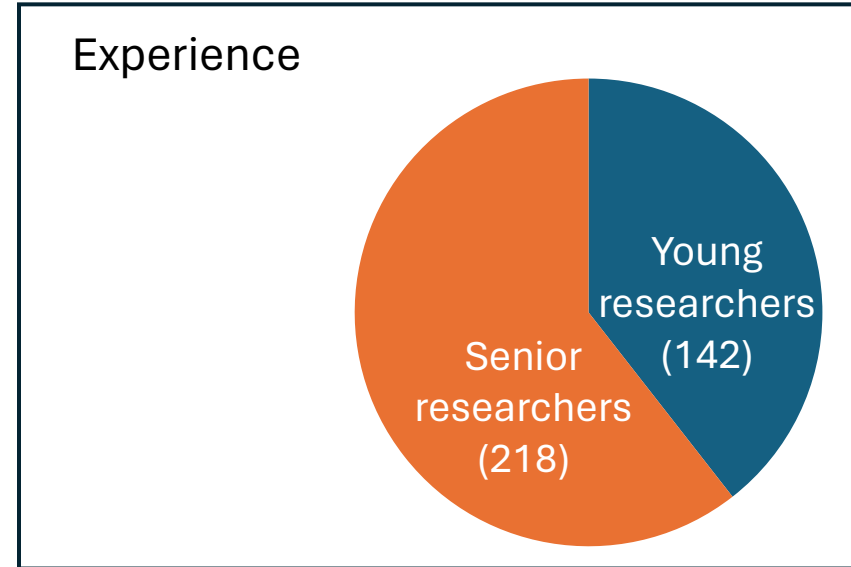
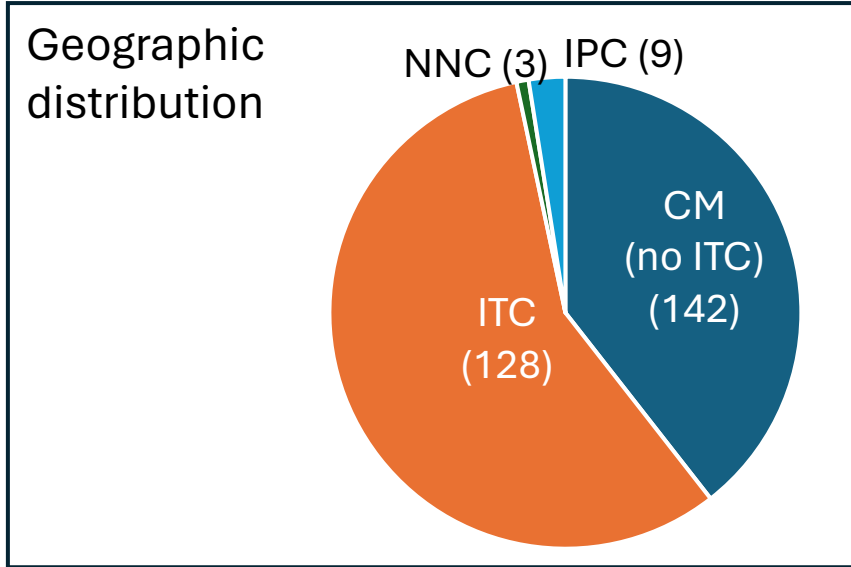
Isabel lastres-Becker (**Spain**)

Core group:

Chair, Vice-Chair, GH scientific representative	3
WG leaders and co-leaders	10
Grant Awarding Coordinator	1
Science Communication Coordinator	1
Gender Equality Officer	1
Total	16

- 7 ITCs
- 11 Women
- 6 Young researchers

Current distribution of 360 participants: 34 countries in MC (19 from ITCs)



Activities

This WG will critically revise basic mechanisms of NRF2 regulation in health and disease from a systems biology perspective, and coordinate the access of the Action members to databases, standard procedures, state-of-the-art technologies and repositories containing high quality customized reagents, validated animal models and biological samples for NRF2 research.

Task

- Elaboration of guidelines with standardized procedures and protocols, and support for data processing and integration
- Organize a toolbox with customized reagents (cells, antibodies, NRF2 modulators, etc.) for advanced studies on the physiopathological function of NRF2.
- Coordinate access to several biobanks which may provide biologic samples from patients with NRF2-related NCDs and matched controls, in compliance with local ethics regulations
- Create a technologic platform based on the technologies and research tools available in the network, including advanced bioinformatics tools for data analysis from the perspective of systems medicine, machine learning and network pharmacology.

Activities

This WG will coordinate all aspects along the pipeline of drug development, including preclinical studies. All the knowledge gathered and tools developed in WG1 will serve to guide the identification of existing and new compounds that target NRF2 and influence the course of selected NCDs in cellular and animal models. WG2 will strive for standardizing procedures and protocols to maximize the reproducibility of results, and for selecting accurate disease animal models.

Task

- Inventory of drugs suitable for repurposing in NRF2 therapeutics
- Inventory of new patented or patentable compounds that target NRF2 and influence the course of various NCDs in cellular and animal models of disease
- Coordinate a virtual repository of superior animal models for various NCDs with pathophysiological processes related to NRF2 deregulation
- Critical analysis of preclinical results on the above mentioned NRF2-modulators in superior animal models.

Activities

This WG will pave the way towards a successful transition from the preclinical to the clinical development of NRF2-targeted compounds. In this stage it is essential to identify reliable NRF2-related biomarkers to monitor disease progression and therapy outcome, equivalent both in patients and animal models. Thus, the main aim of WG3 will be to elaborate the template for future clinical trials on lead compounds identified in WG2 and to coordinate NRF2-related genetic and biochemical biomarker discovery in the selected NCDs.

Task

- Identification of NRF2-related genetic and biochemical biomarkers using available databases of NCD patients and, in collaboration with WG2, identification of animal models of NCDs that faithfully replicate these human biomarkers.
- Documentation of the panel of somatic mutations in the KEAP1/NRF2 system in non-small lung cancer that can be detected by cfDNA.
- Documentation of clinical NFE2L2 genetic variants and endophenotypes, as well as drug response/resistance phenotypes of patients suffering from the subset of NCDs where NRF2 alterations have been identified;
- Documentation of NRF2-related blood biomarkers and the design of a clinically-relevant biochip
- Elaboration of the preliminary documentation for future clinical trials with compounds identified in WG2, that demonstrate efficacy in relevant animal models that replicate alterations in NRF2 pathophysiology.

Activities

As mentioned before, Europe is losing leadership and competitiveness in NRF2-related pharmacology since products initially developed in Europe are being exploited in third countries. In this context, this WG will design the strategy to retain innovation and facilitate the transfer of knowledge to European industry by building bridges between academia and industry, and provide training and advice in knowledge/technology transfer and entrepreneurship to the next-generation researchers.

Task

- Identification and active diffusion of BenBedPhar capabilities.
- Identification and attraction of additional SMEs to the Action.
 - Elaboration of procedures, list of lead compounds, drug delivery systems, blood-based biomarkers for clinical implementation, or other technologic outcomes
- Reinforce the BenBedPhar-industry cooperation by organizing 3 industry showcase events.

Working group 5: WG5: Outreach and dissemination

Activities

This WG will globally coordinate the exchange of knowledge, tools and results within the Action for maximizing the visibility of the Action to different stakeholders: general public, patient associations, researchers, pharmaceutical industry, clinicians, and policy makers. The content and format of the messages will be carefully adapted to the type of audience. This WG will be essential to reinforce and consolidate the collaborations of the major players in the NRF2 field and drug discovery with policy makers and other stakeholders, and to assure the sustainability of the network beyond the Action through a functional network.

Task

- Development of the BenBedPhar webpage
 - Identification of relevant social networks and events for promoting NRF2-related medicine and limitations in the lay public
- Organization of a yearly “BenBedPhar Open Day”.
- Coordination of joint publications/communications, newsletters, presence in social networks, etc.
- Identification of funding opportunities for sustaining research and drug development (public and private funding calls).

1. Knowing each other during the scientific meeting of COST Action CA20121. On line. January 10-11, 2022.
2. Translating NRF2 research from bed to bench. Madrid, Spain. May 19-21, 2022.
3. Bench to Bedside for Pharmacological regulation of NRF2 in no communicable diseases. Bucharest, Romania. October 13-14, 2022
4. From Physiology to Pathology. Zagreb, Croatia. April 20-21, 2023.
5. Translating NRF2 research into clinical practice. Graz, Austria. October 12-13, 2023.
6. Building bridges between academy and industry around NRF2-based therapeutics. Athens, Greece. February 8-9, 2024.
7. Cellular Mechanisms, Disease Modeling and Clinical Approaches to NRF2 Therapeutics. Tallinn, Estonia. April 18-19, 2024.
8. Next Lisbon, Portugal October 2024

1. Impact of Keap1/Nrf2 signaling on thyroid physiology and disease
2. Targeting the NRF2/beta-TrCP axis in liver disease
3. The role of NRF2 for mitochondrial adaptation
4. Identifying NRF2 vulnerabilities in NRF2-dependent cancers
5. To orchestrate S-nitrosylation; a novel function of the KEAP1 redox sensor
6. Electrophile and protein-protein interaction inhibitors of Keap1
7. NRF2 and Peroxiporins. Can they modulate cancer resistance?

1. Novel atypical functions of NRF2 in endothelial cells
2. The XVth International congress of Toxicology
3. Europhysiology 2022 meeting

Three ITC grants to attend the training school of the SFRR-E Spetses, Greece. September 2024.

1. Modulation of synaptic fitness by NRF2
2. Wire myography training
3. Understanding the complexities of NRF2 dynamics under physiological normoxia
4. Polyphenols and their sulfated metabolites as potential regulators of NRF2
5. Unravelling the role of NRF2 in hepatic insulin resistance
6. The role of NRF2 in Lama2-deficiency
7. NRF2 as a novel therapeutic target in age related macular degeneration
8. Is aquaporin activity affected by Nrf2 activation?
9. In silico analysis of a HPM library for NRF2 activators identification

1. NRF2 in noncommunicable diseases: from bench to bedside. Smolenice, Slovakia. June 26 - 30, 2023. (30 participants)
2. Physiological oxygen levels to investigate NRF2 regulated redox signaling in cell biology to improve clinical translation. London, UK, March 5 - 8, 2024. (15 participants)
3. Next: NRF2 network – molecules, pathways, and mechanisms. Wieliczka, Poland. June 24-28, 2024 (expected 30 participants).

Newsletters:



Issue 8, January 2024

NRF2 in COST Action 20121 Our quarterly newsletter attempts to provide our latest news and also aims at becoming a forum for analysis of relevant



Issue 7, October 2023

NRF2 in COST Action 20121 Our quarterly newsletter attempts to provide our latest news and also aims at becoming a forum for analysis of relevant



Issue 6, April 2023

NRF2 in COST Action 20121 Our quarterly newsletter attempts to provide our latest news and also aims at becoming a forum for analysis of relevant



Issue 5, January 2023

NRF2 in COST Action 20121 Our quarterly newsletter attempts to provide our latest news and also aims at becoming a forum for analysis of relevant



Issue 4, October 2022

NRF2 in COST Action 20121 Our quarterly newsletter attempts to provide our latest news and also aims at becoming a forum for analysis of relevant



Issue 3, July 2022

NRF2 in COST Action 20121 Our quarterly newsletter attempts to provide not only our latest news but also aims at becoming a forum for analysis



Issue 2, April 2022

NRF2 in COST Action 20121 Our quarterly newsletter attempts to provide not only our latest news but also aims at becoming a forum for analysis



Issue 1, January 2022

NRF2 in COST Action 20121 Since the start of BenBedPhar in November 2021, I would dare to say that our activity has been more than

[READ MORE](#)



In collaboration with Sapienza University
Prof. Luciano Saso; Prof. Brigitta Buttari

1. NRF2 and Cancer. March 3rd, 2022
2. NRF2 and vascular diseases. April 26th, 2022
3. NRF2 and metabolic diseases. July 7th, 2022
4. NRF2 and System medicine. March 10th, 2023
5. NRF2 and Neuroinflammation. June 12, 2023
6. NRF2 and Autoimmunity. January 19, 2024
7. **Next:** Oxidative stress and Aging. May 14, 2024



Dr. Roberta Foresti
(University Paris Est Créteil)

1. Introduction to Podcast - about enzymes & molecules. Roberta Foresti
2. Heme Oxygenase & Carbon Monoxide - Dr. Leo Otterbein
3. Bilirubin - Dr. Roland Stocker
4. Pharmacological regulation of NRF2. Albena Dinkova-Kostova
5. Next: NRF2 in physiology and pathology. Antonio Cuadrado

July 6th 7th, 2022



September 7th, 2023



Next: September 2024

Over 40 co-authored publications after two grant periods

Introduction to Special Issue on "Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases"
By: Cuadrado A, Dinkova-Kostova AT, Mann GE

Protective actions of nuclear factor erythroid 2-related factor 2 (NRF2) and downstream pathways against environmental stressors
By: Bayo Jimenez MT, Frenis K, Hahad O, Steven S, Cohen G, Cuadrado A, Münzel T, Daiber A

Personalized redox medicine in inflammatory bowel diseases: an emerging role for HIF-1 α and NRF2 as therapeutic targets
By: Bourgonje AR, Grochot-Przećek A, Feelsch M, Cuadrado A, van Goor H

KEAP1-NRF2 protein-protein interaction inhibitors: Design, pharmacological properties and therapeutic potential
By: Crisman E, Duarte P, Dauden E, Cuadrado A, Rodríguez-Franco ML, López MG, León R

The current status and future prospects for therapeutic targeting of KEAP1-NRF2 and β -TrCP-NRF2 interactions in cancer chemoresistance
By: Srivastava R, Fernández-Ginés R, Encinar JA, Cuadrado A, Wells G

Repeat Pathology -ALS Is Associated with Mitochondrial and NRF2 Pathway Imbalance
By: Kirby J, Mata MR, Malaspina O A, Rojo AI

ALS-FTD spectrum
By: Isabel Lastres-Becker, Eva de Lago, Ana Martínez and Javier Fernández-Ruiz

Defining roles of reactive oxygen species (ROS) in cell biology physiology
By: Helmut Sies, Vsevolod Belousov, Navdeep S. Chandel, Michael J. Davies, Dea Giovanni E. Mann, Masayuki Yamamoto, Wouter J. van der Vliet

Role of Inflammation and Redox Status on Doxorubicin-Induced Cardiotoxicity in Infant and Adult CD-1 Male Mice
By: Reis-Mendes A, Padrão AI, Dória J, Gonçalves-Monteiro S, Duarte Araújo M, Remão F, Carvalho F, Sousa E, Bastos ML and Costa T

SH-29 and SK-119 Attenuates Air-Pollution Induced Damage by Activating Nrf2 in HaCaT Cells
By: Sarmistha Saha, Brigitta Buttarl, Elisabetta Profumo, Paolo Tucci, Luciano Saso

A Perspective on Nrf2 Signaling Pathway for Neuroinflammation: A Potential Therapeutic Target in Alzheimer's and Parkinson's Diseases
By: Sarmistha Saha, Brigitta Buttarl, Elisabetta Profumo, Paolo Tucci, Luciano Saso

Hepato-renal toxicity of low dose metal(oid)s mixture in real-life risk simulation in rats: Effects on Nrf2/HO-1 signalling and redox status
By: Vukelić D, Baralić K, Marić D, Đukić-Čosić D, Bulat Z, Panjari E, Saso L, Djordjević AB

Emerging roles of Keap1/Nrf2 signaling in the thyroid gland and perspectives for bench-to-bedside translation
By: Chartoumpekis DV, Ziros PG, Habeos IG, Sfyriotis GP

NF2 signaling in cancer
By: Gorgieva Ackova D, Maksimova V, Smilov K, Buttari B, Arese M, Saso L

Alkaloids as Natural NRF2 Inhibitors: Chemoprevention and Cytotoxic Action in Cancer
By: Gorgieva Ackova D, Maksimova V, Smilov K, Buttari B, Arese M, Saso L

Redox Regulation of Microglial Inflammatory Responses: Fine Control of NLRP3 Inflammasome through Nrf2 and NOX4
By: Palomino-Antolin A, Decouty-Pérez C, Parré-Alins V, Narros-Fernández P, Lopez-Rodriguez AB, Álvarez-Rubial M, Valencia I, López-Muñoz F, Ramos E, Quintana-Casas AI

The NRF2/Keap1 pathway as a therapeutic target in inflammatory bowel disease
By: Geertsema S, Bourgonje AR, Fagundes RR, Gacesa R, Weersma RK, van Goor H, Mann FE, Dijkstra G, Faber KN

The Role of Nrf2 and Inflammation on the Oxidative Stress in Cardio-Oncology In vivo Study Through Time
By: Reis-Mendes A, Ferreira M, Rojo AI, Duarte JA, Duarte-Araújo JM, F. Carvalho F, Sousa E, Costa VM

Oxidative Stress as a Regulatory Checkpoint in the Production of Antiphospholipid Autoantibodies: The Protective Role of NRF2 Pathway
By: Sorice M, Profumo E, Recalco G

Nrf2 depletion in the liver leads to loss-of-function of antioxidant enzymes and mitochondrial dysfunction
By: Dayalan Naidu S, Angel Knatko EY, Legnardi C, Novakova L, Vega L, Ganley IG, Abramov A, Dinkova-Kostova AT

Whole Blood Expression Pattern of Inflammation and Redox Genes in Mild Alzheimer's Disease
By: Elena Milanese, Maria Dobre, Cătălina Anca Cucos, Ana I Rojo, José Jiménez-Villegas, Estibaliz Capetillo-Zarate, Carlos Matute, Gerard Piñol-Ripoll, Gina Manda, and Antonio Cuadrado

The Transcription Factor NRF2 Has Epigenetic Regulatory Functions Modulating HDACs, DNMTs, and miRNA Biogenesis
By: Silveira-Linares I, Shin C-H, Jiménez-Villegas J, Gorgieva M, Lastres-Becker I

Advances and challenges in therapeutic targeting of NRF2
By: Dinkova-Kostova AT, Coppel IM

An Overview of NRF2-Activating Compounds Bearing α,β -Unsaturated Moieties and Their Antioxidant Effects
By: Egbujor MC, Buttari B, Profumo E, Telikoukian-Akhalilov D, Saso L

NRF2: A crucial role in mitochondrial metabolism and prostate cancer progression
By: Buttari B, Arese M, Obermüller M, Deegan RE, Saso L, Chatterjee S

An inhibitor of interaction between the transcription factor NRF2 and the E3 ubiquitin ligase adapter β -TrCP delivers anti-inflammatory responses in mouse liver
By: Fernández-Ginés R, Encinar JA, Hayer JD, Oliva B, Rodríguez-Franco ML, Rojo AI, Cuadrado A

Overlooked and valuable facts to know in the NRF2/KEAP1 field
By: Ana Rojo, Aleksandra Piechota-Polanczyk, Antonio Cuadrado, Ana Grochot-Przećek

Personalized redox medicine in inflammatory bowel diseases: an emerging role for HIF-1 α and NRF2 as therapeutic targets
By: Bourgonje AR, Grochot-Przećek A, Feelsch M, Cuadrado A, van Goor H

Altered Blood and Brain Expression of Inflammation and Redox Genes in Alzheimer's Disease, Common to APPV717 x TAU P301L Mice and Patients
By: Cucos CA, Milanese E, Dobre M, Musat IA, Manda G, Cuadrado A

Co-exposure to urban particulate matter and aircraft noise adversely impacts the cerebral pulmonary-cardiovascular axis in mice
By: Kuntić M, Kuntić I, Kirić R, Gerićke A, Oelze M, Jurić B, Bayo Jimenez MT, Stanić Nandudu M, Hahad O, Kuntić M

The Triterpenoid Nrf2 Activator, CDDO-Me, Decreases Neurophilin Senescence in a Murine Model of Joint Damage
By: Amirova KM, Dimitrova PA, Leseva MN, Koycheva IK, Dinkova-Kostova AT, Gorgieva MI

Drug repurposing on Alzheimer's disease through modulation of NRF2 signaling in the neighborhood
By: Bourdakou MM, Fernández-Ginés R, Cuadrado A, Spyrou GM

The Triterpenoid Nrf2 Activator, CDDO-Me, Decreases Neurophilin Senescence in a Murine Model of Joint Damage
By: Amirova KM, Dimitrova PA, Leseva MN, Koycheva IK, Dinkova-Kostova AT, Gorgieva MI

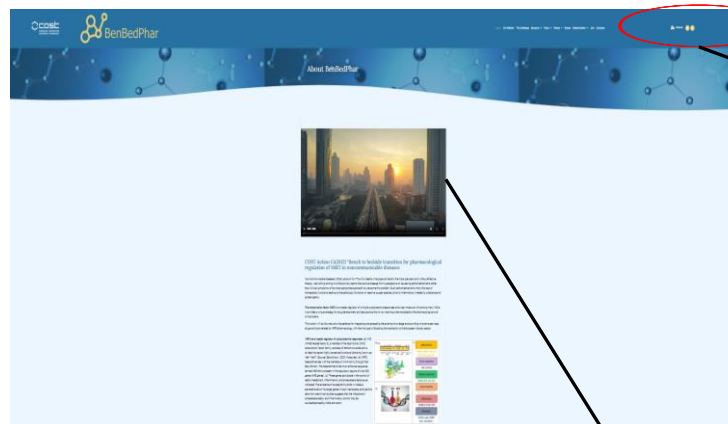
#	Title	Countries participating in the Action among proposers	Main proposer name	Funder	Amount	Call identifier	Relevance to H2020 Societal Challenge
1	NRF2 as a novel therapeutic target in early and intermediate age-related macular degeneration	PT, ES	Miguel Seabra	Other EU	985012 €	HR22-00569	Health, demographic change and wellbeing
2	Investigation of the effects of SK-119 and SH-29 pharmacological agents on the Nrf-2 pathway in an in vitro and in vivo atopic dermatitis model	IL, TR	Cagatay Karaaslan	National	41675 €	TUBITAK- 2515 COST	Health, demographic change and wellbeing
3	Investigation of NRF2 regulation molecules on scleroderma	TR	Ayşe Kocak Sezgin	National	44000 €	TUBİTAK-2515 COST	Health, demographic change and wellbeing
4	In search of a peripheral reliable and highly predictive immuno-metabolic signature for the diagnosis and management of uni- and bipolar affective disorders	IT	Alessandra Berry	National	1000000 €	PNRR:M6/C2_CALL	Health, demographic change and wellbeing
5	Development of SIMOA-based kit to determine Nrf2 level and activity	TR	Sibel Kalyoncu Uzunlar	National	33100 €	TUBITAK 2519 COST	Health, demographic change and wellbeing
6	Keap1-dependent proteopathy as a unifying mechanism of	PL	Anna Grochot-Przeczek	National	554000 €	NCN OPUS 22	Not Applicable

7	Rational design of peptides targeting BTB domain homodimerization of BACH2, a nuclear suppressor NRF2 transcription factor: Complementary in silico and in vitro approaches	TR	Ahmet Can Timucin	National	31000 €	Tubitak 2515 COST	Health, demographic change and wellbeing
8	Genetic and molecular bases of sensorineural deafness and hearing damage: exploration of new targets and therapeutic strategies	ES	Isabel Varela Nieto	National	266200 €	MCIN/AEI/10.13039/501100011033	Health, demographic change and wellbeing
9	PAS GRAS: de-risking metabolic, environmental and behavioral determinants of obesity in children, adolescents and young adults	DE, IT, PL, PT, ES, SE, UK	Paulo Oliveira	Trans-national	9500000 €	HORIZON-HLT H-2022-STAYH LTH-01-two-stage	Health, demographic change and wellbeing
10	Anti-inflammatory activity of Lupeol loaded nanoparticles to counteract 7-Ketocholesterol-induced oxiaoptophagy in human macrophages: potential therapeutic implications in Atherosclerosis	IT	Brigitta Buttari	National	100000 €	Bando Ricerca Indipendente ISS "Terza edizione (2023))	Health, demographic change and wellbeing
11	Effect of NRF-2 activation in cholesterol induced in vitro lipid accumulation and in vivo NASH models	TR	Nesrin Kartal Ozer	National	57000 €	Tubitak 2515-COST Action support	Health, demographic change and wellbeing
12	MINA-CM Madrid Innovative Neurotech Alliance	ES	Gustavo Guinea	National	827000 €	P2022/BMD-7236	Health, demographic change and wellbeing
13	Targeting the transcription factor NRF2 for synaptic protection in tauopathies	ES	Antonio Cuadrado	National	300000 €	PROYECTOS DE GENERACIÓN DE CONOCIMIENTO 2022	Health, demographic change and wellbeing

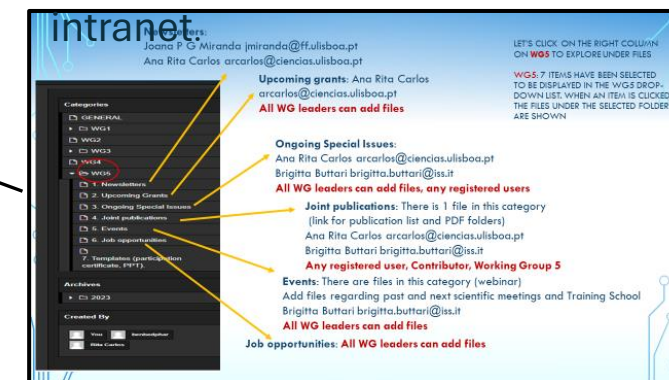
Dissemination



✓ **Action website**
<https://benbedphar.org/>



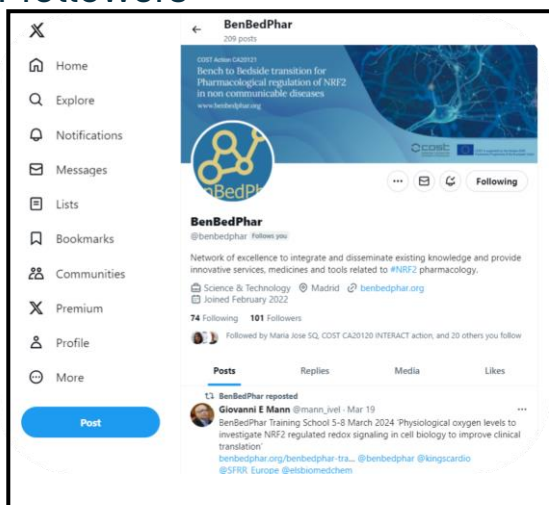
✓ **BenBedPhar INTRANET:**
All COST Action members have been granted access to the intranet.



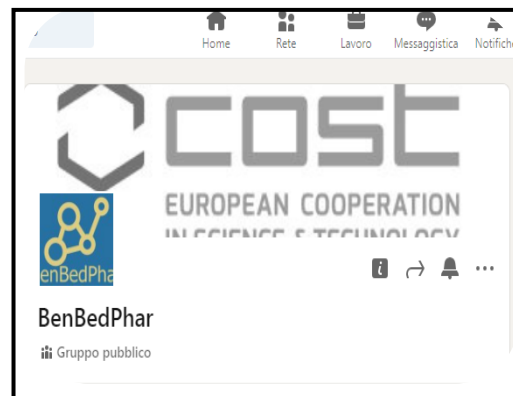
@BenBedPhar
official social media groups

✓ **Mail list**

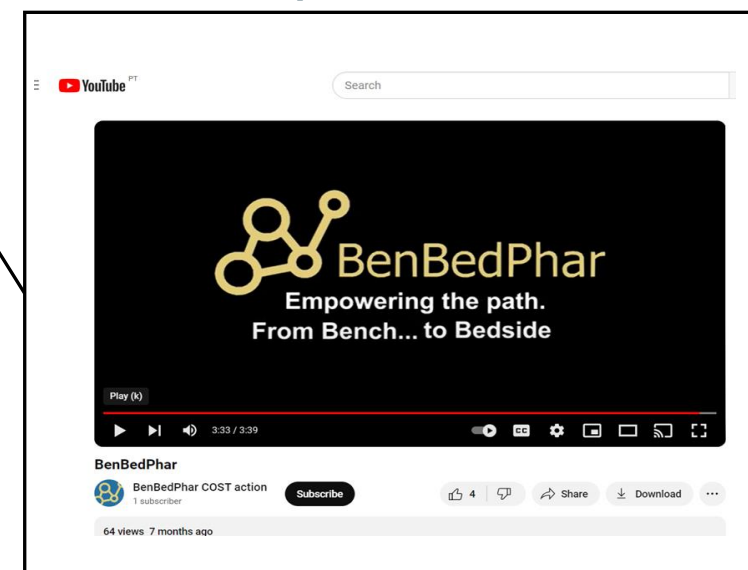
✓ **Tweeter**
101 followers



✓ **LinkedIn**
76 members



✓ **BenBedPhar promotional video: 64 views**



SWOT

Strengths:



- 360 participants
- Main researchers globally
- Proactivity of senior participants

Weaknesses:



- Low engagement of young researchers
- Low participation WG4: economical exploitation

Opportunities:



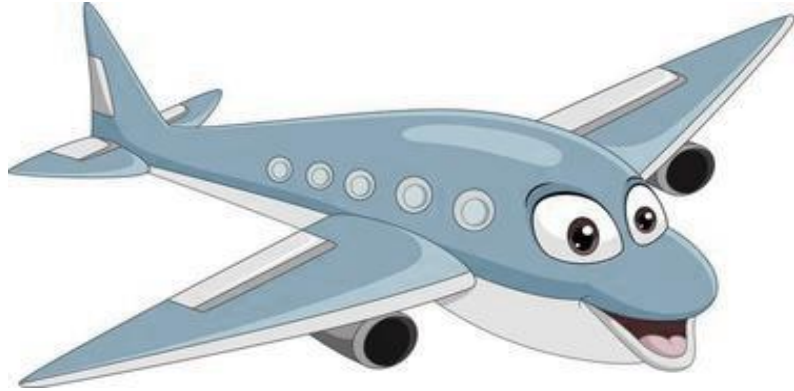
- Grant applications
- Publications
- SMEs

Threats:



- Lack of impact on clinical development
- Low impact on economic exploitation

Sustainability



- More interaction with industry
- Increase recruitment of research clinicians
- More joint grant applications
- Coordination with young researchers

Thank you!

<https://benbedphar.org/>