

June 26 - 30, 2023
Smolenice Castle,
Slovakia

BenBedPhar Training School 2023

NRF2 in non-communicable diseases: From bench to bedside

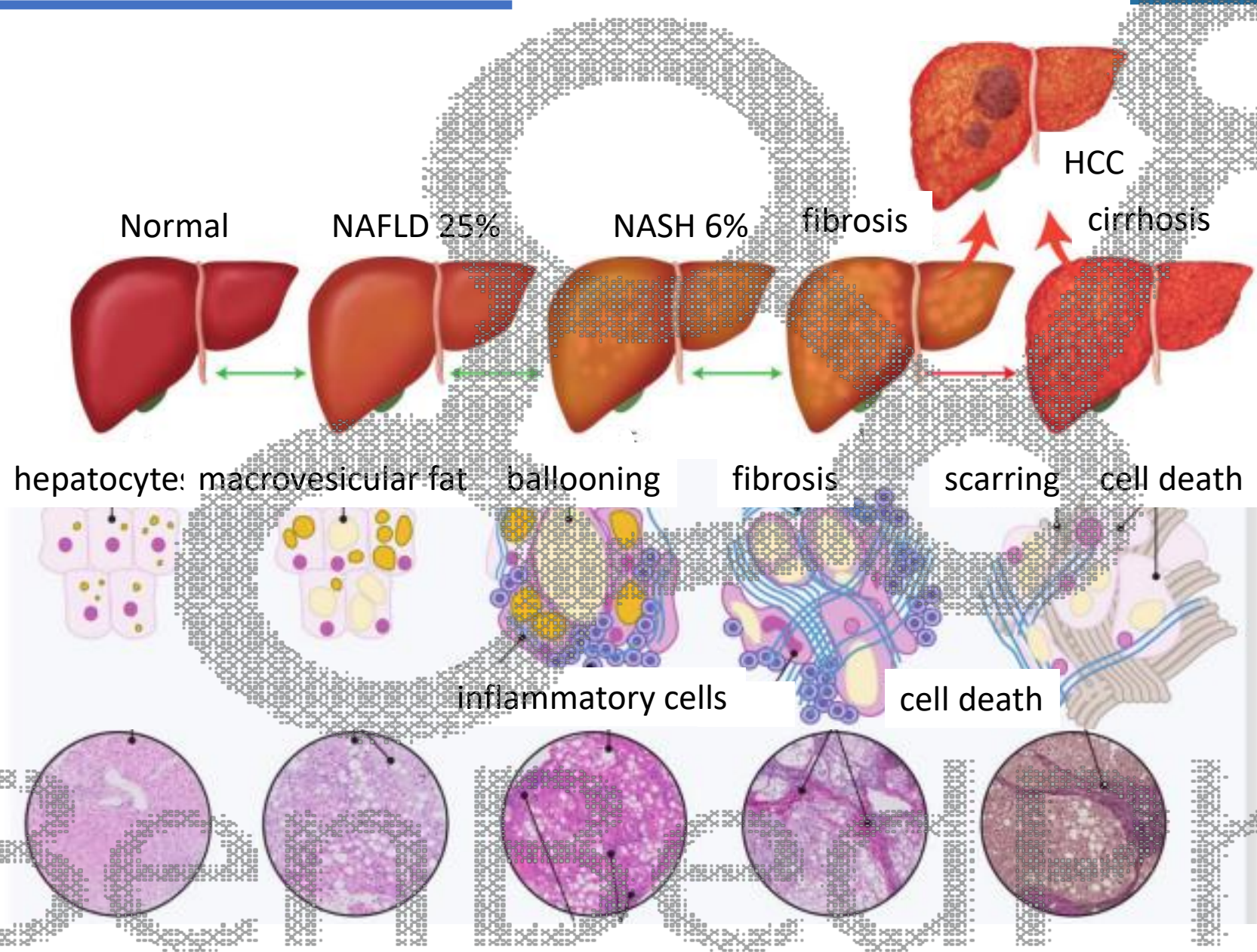


NRF2 in liver diseases

Prof. Antonio Cuadrado

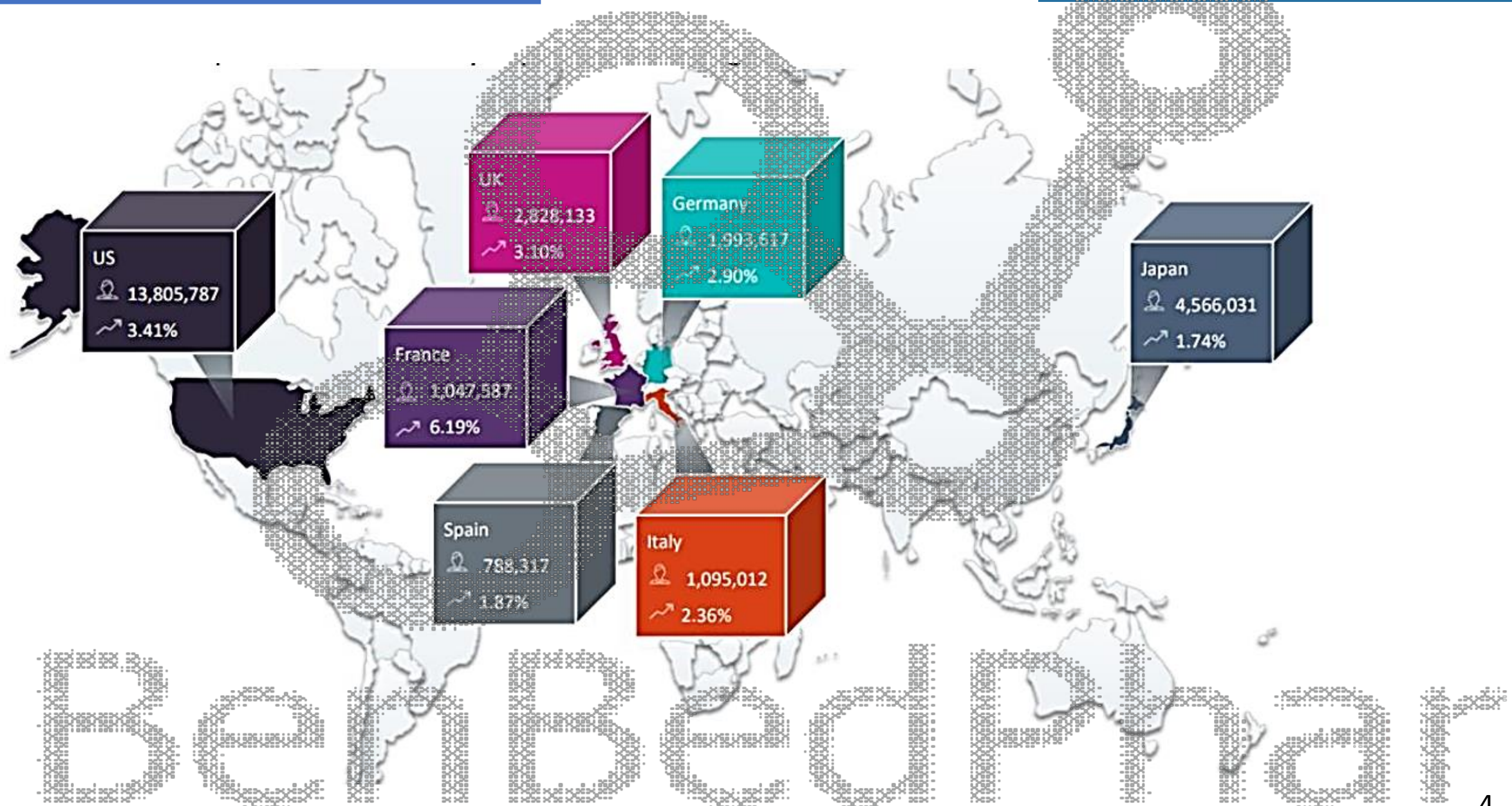
Department of Biochemistry, Medical College,
Autonomous University of Madrid, Spain

Progression of fatty liver towards liver failure



Modified from Ruissen et al, Eur J Enzymol 2020.

NAFLD prevalence



Cemetry for drugs that have failed in NASH therapy

Table 1. Drugs that have been (temporarily) withdrawn from seeking marketing authorization for NASH.

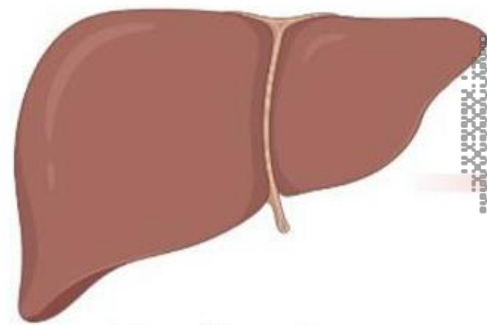
Company	Drug	Drug class	Phase	Reason	Date of announcement of discontinuation
Gilead	Selonsertib	ASK1 inhibitor	3	Lack of efficacy	2/11/2016
Gilead	Simtuzumab	LOXL2 neutralizing antibody	2	Lack of efficacy	2/11/2016
Cempra	Solithromycin	CCL24 neutralizing antibody	1	Hepatotoxicity	28/2/2017
Astra Zeneca	AZD4076 (RG-125)	Anti micro RNA-103/107	1/2a	Unclear	12/6/2017
Gilead	Firsocostat (monotherapy)	Acetyl-CoA carboxylase (ACC1/ACC2) inhibitor	3	Efficacy	16/12/2019*
Gilead	Cilofexor (monotherapy)	Farnesoid X receptor agonist	3	Efficacy	16/12/2019*
Boehringer Ingelheim	BI 1467335	Amine oxidase copper-containing 3 (AOC3) inhibitor	2	Drug-drug interactions	18/12/2019
Conatus	Emricasan	Pan-caspase inhibitor	2b	Efficacy	24/6/2019
Genfit	Elafibranor	PPAR- α/δ agonist	3	Efficacy	23/7/2020
TaiwanJ Pharmaceuticals	JKB-121	Toll like receptor 4 antagonist	2	Efficacy	19/4/2018
Temporary halt					

Lack of approved therapies for NASH, a huge unmet medical need

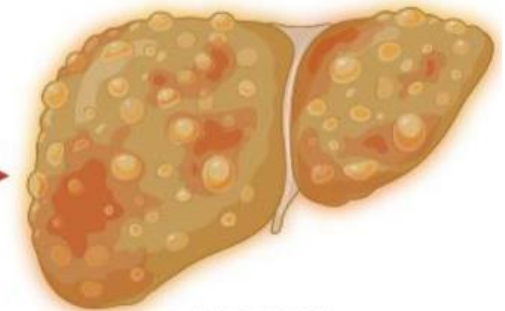
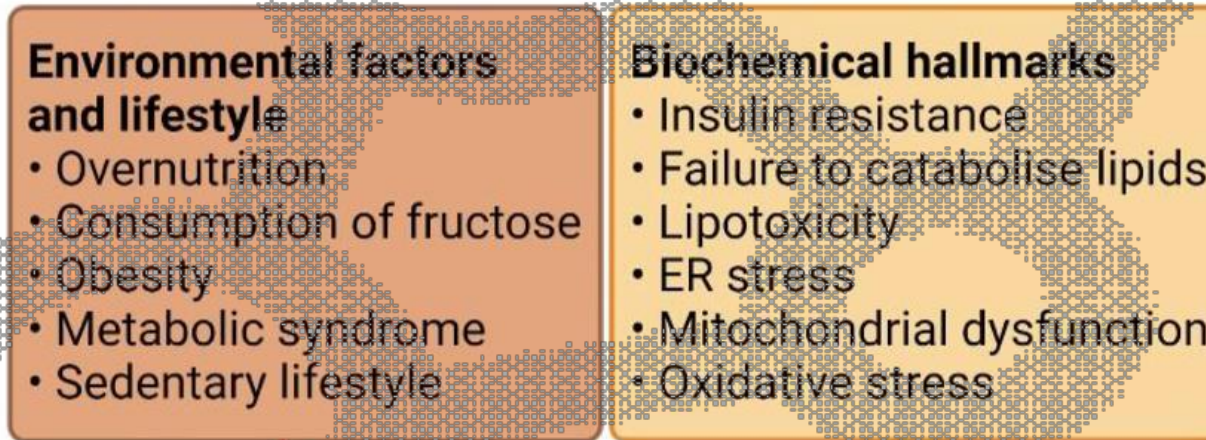
NASH may be regarded as a syndrome



John D. Hayes
University of Dundee
UK

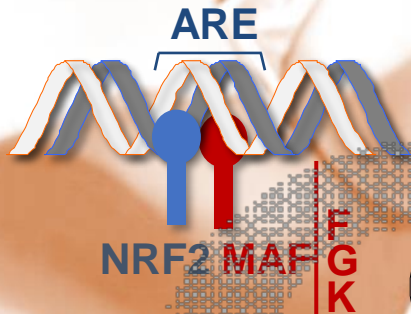
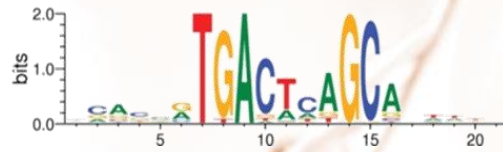


Healthy liver



NASH

NRF2: master regulator of cell homeostasis



Redox balance

Inflammation

Lipid metabolism

Redox balance

HMOX1, NQO1, TrxR, cGS,
GCLc, GCLm, Gpx, GR ...

Purine metabolism

PPAT, MTHFD2

Pentoses metabolism

GGPDH, PGD, IDH1, ME

Lipid metabolism

ACC1, FAS, SCD1, ACL...

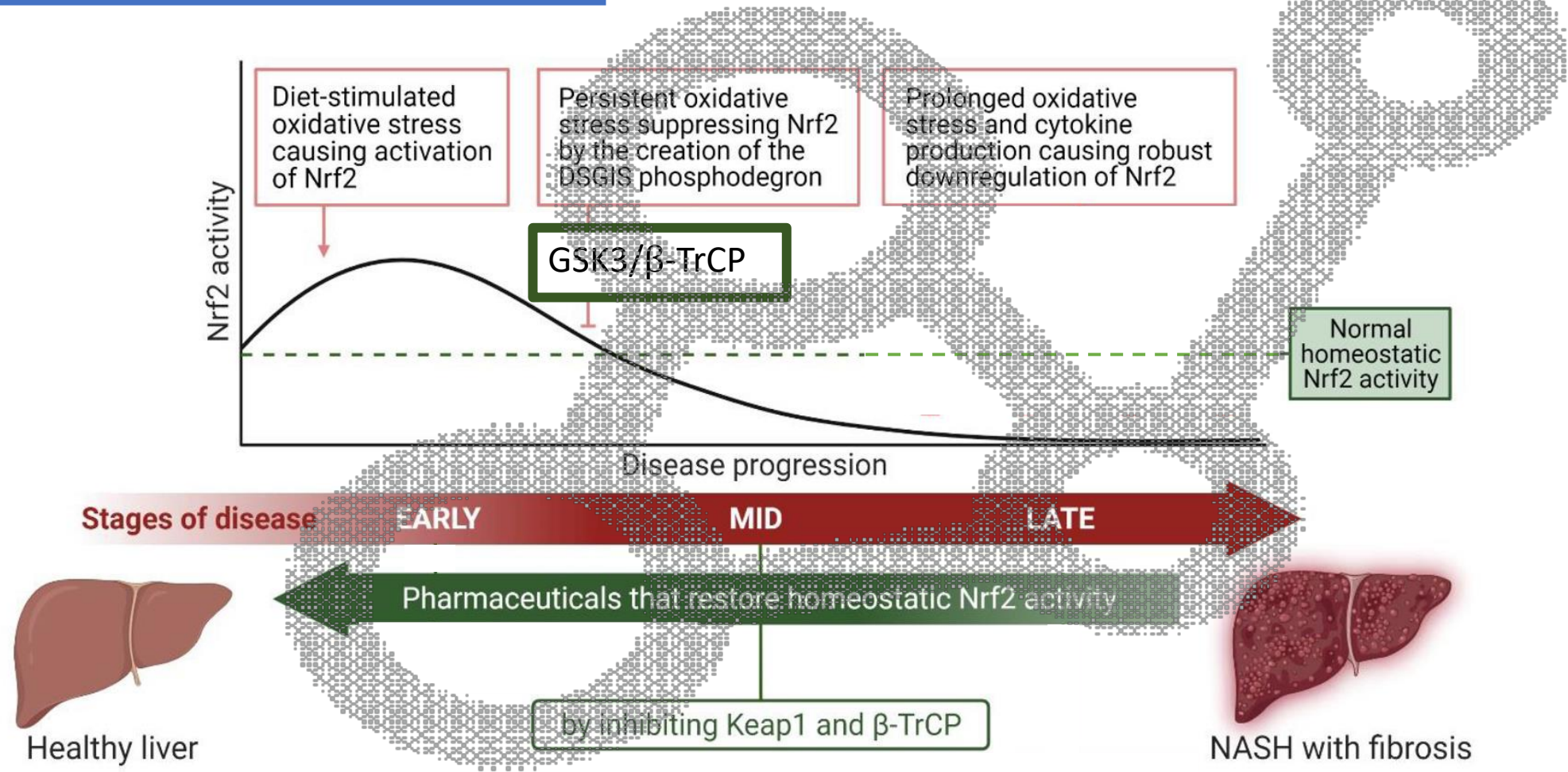
Inflammation

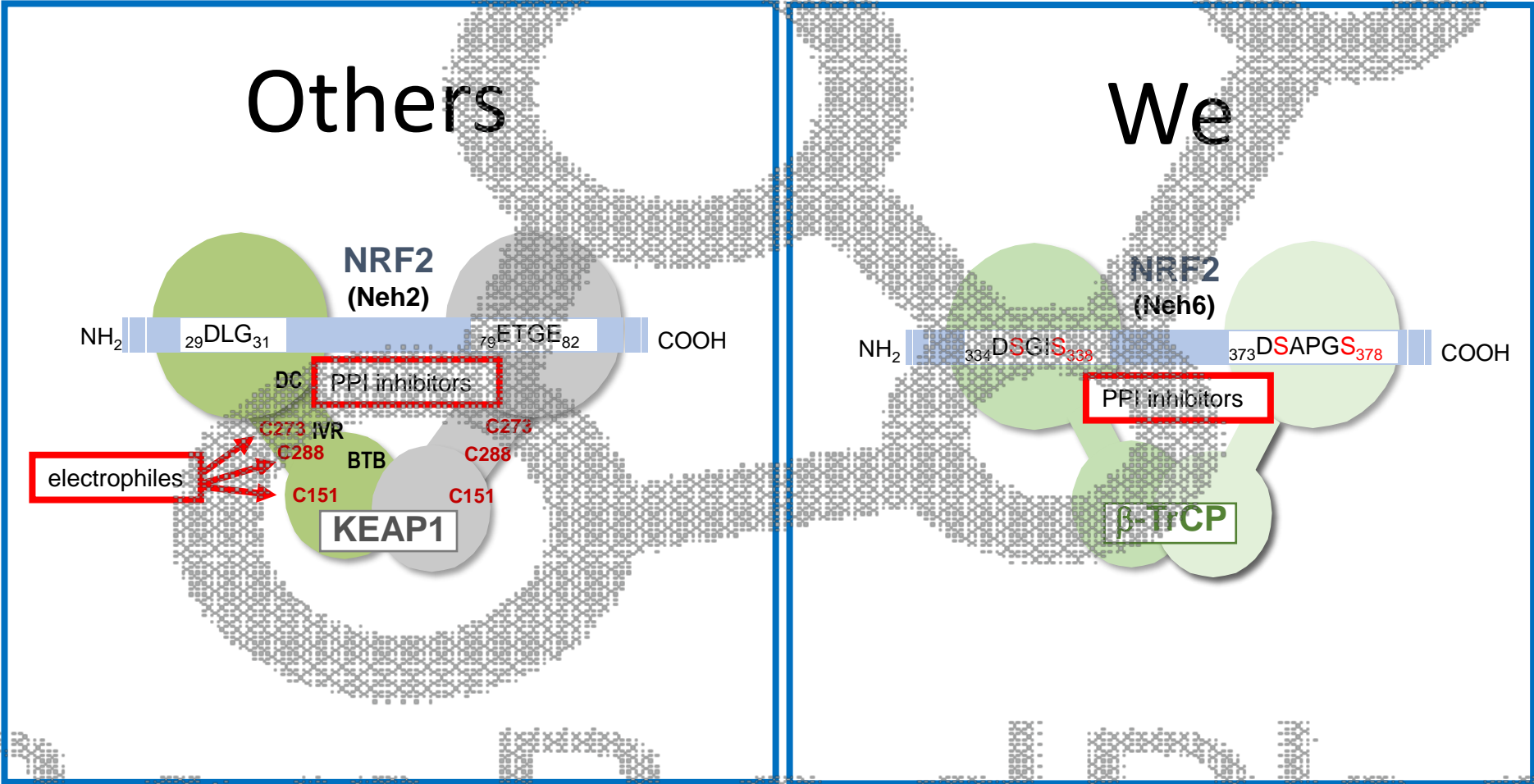
MARCO, CD36, IL17D

Proteostasis

Gpx8, PSMB7, SQSTM1,
CALCO2, ULK1

NRF2-based therapeutic strategies for NASH therapy





Chemical libraries

ZINC natural products and SuperNatural II

First Filter:

Molecular docking to IP22
 $\Delta G < 9.5$ Kcal/mol

Molecular docking
Autodock/Vina

473 compounds

Second Filter:

LogP, LogS, Drugscore, druglikeness,
Ro5 violations, HBA, HBD, rat acute toxicity,
mutagenic, etc.

ADMET profiles
Data Warrior & admetSAR

87 compounds

Third Filter:

Dynamics simulation over 200 ns

Molecular Dynamics
YASARA

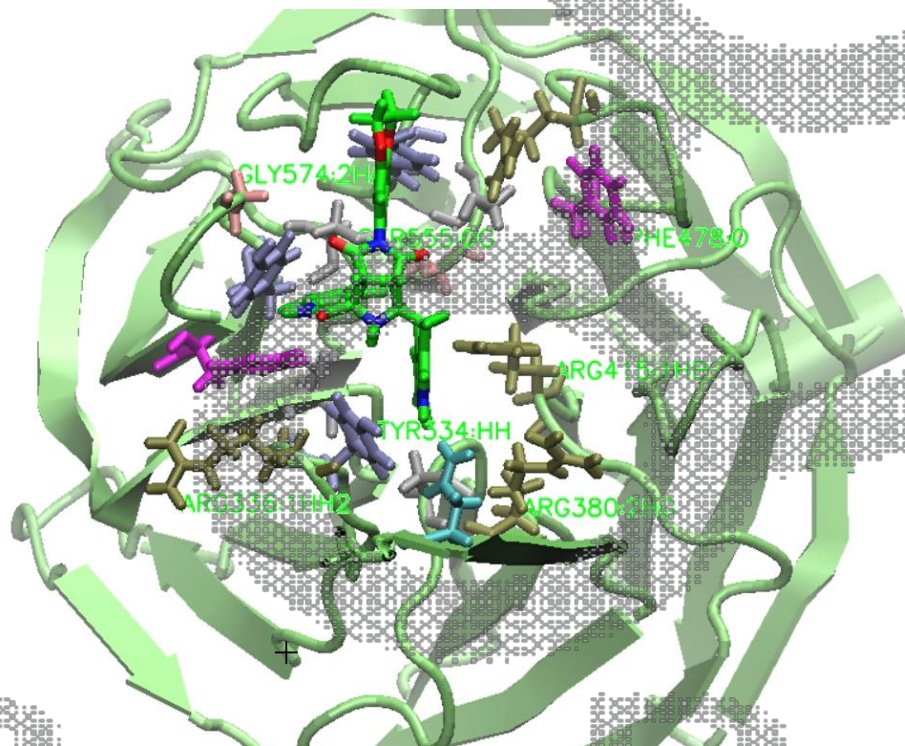
30 compounds



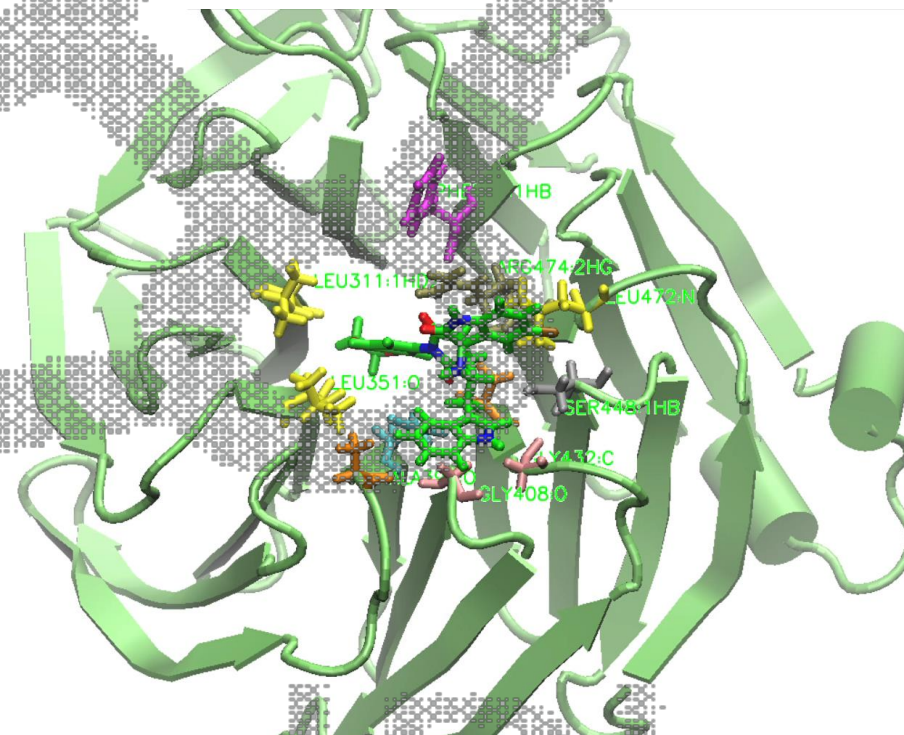
Dr. José Antonio Encinar
University Miguel Hernández
Alicante
Spain

PHAR theoretically inhibits β -TrCP but not KEAP1

PHAR / KEAP1

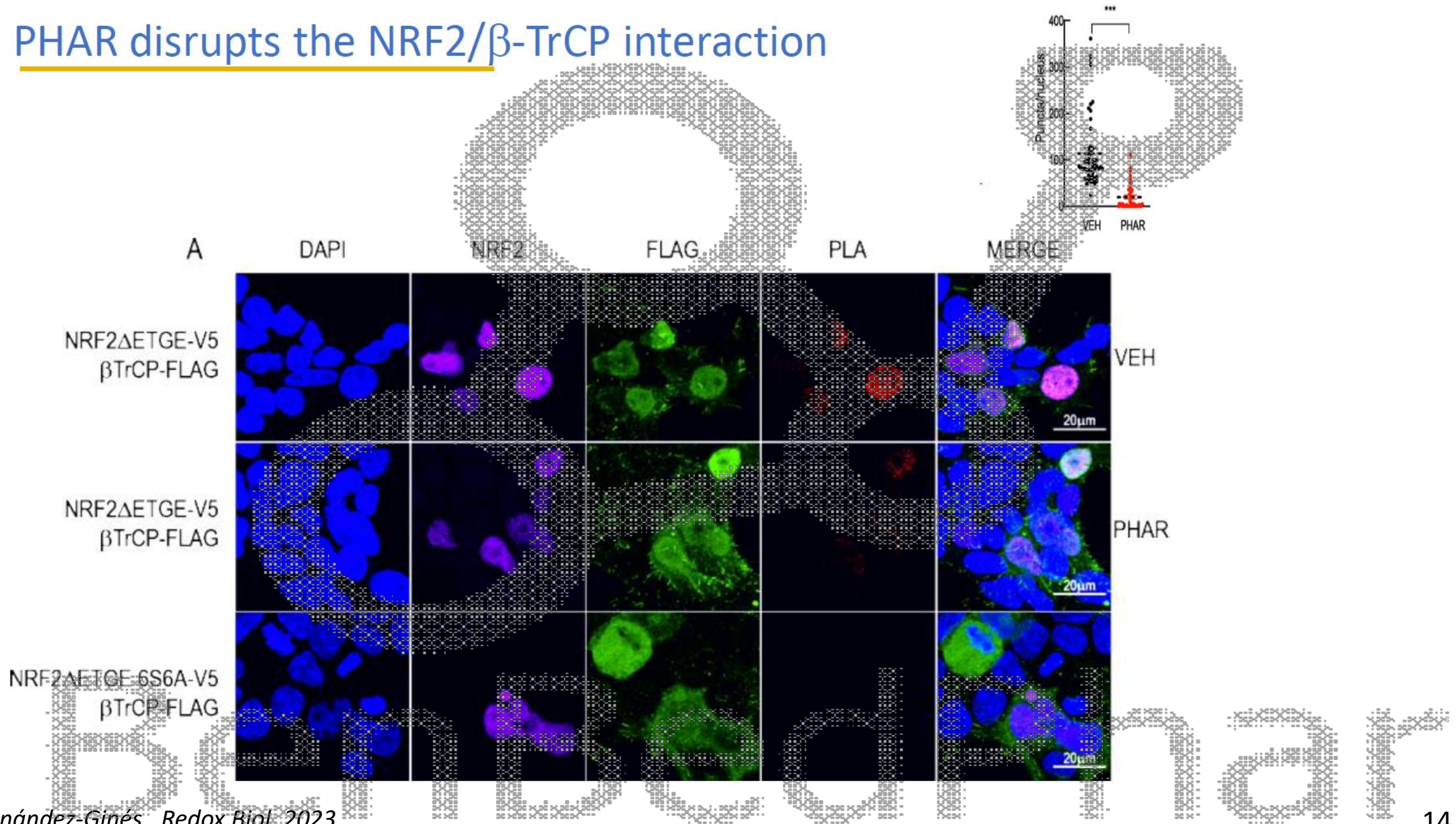


PHAR / β -TrCP

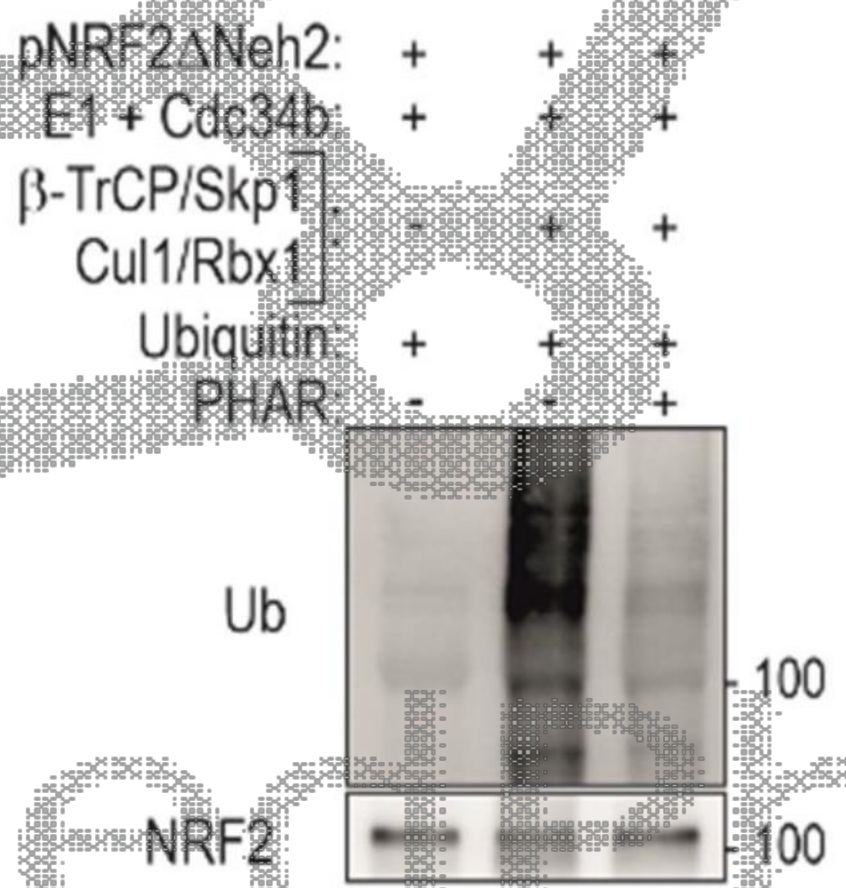
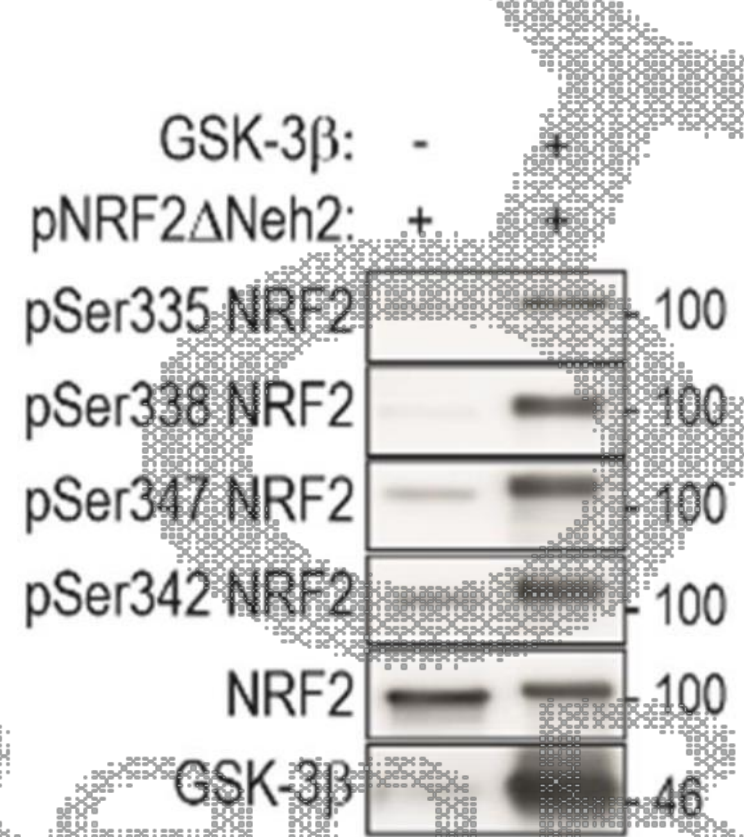
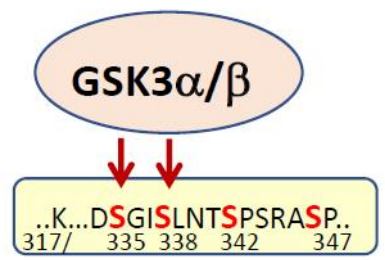


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PHAR disrupts the NRF2/ β -TrCP interaction



PHAR prevents the TrCP-mediated ubiquitilation of NRF2

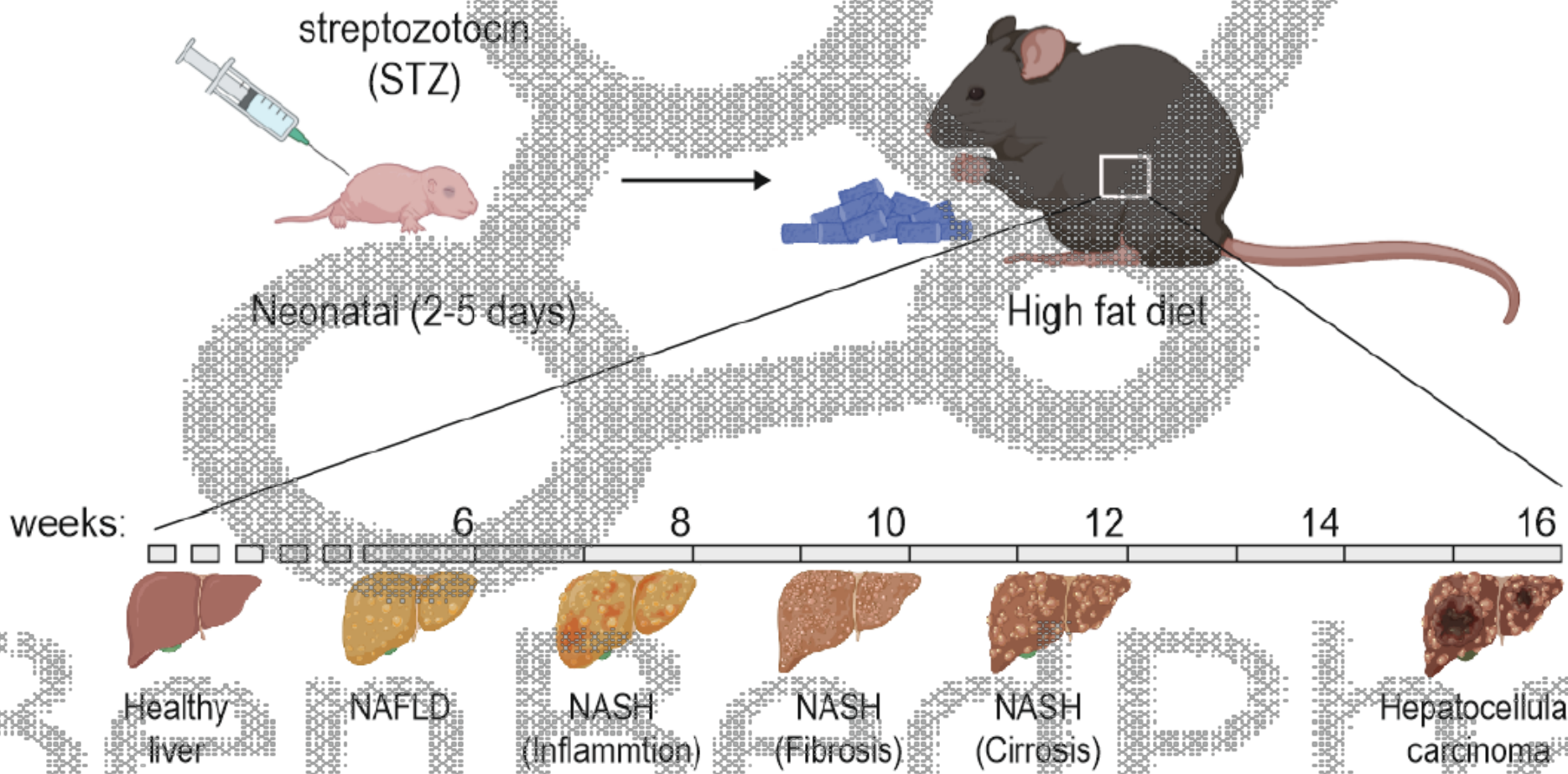


PHAR activates NRF2 in mouse liver

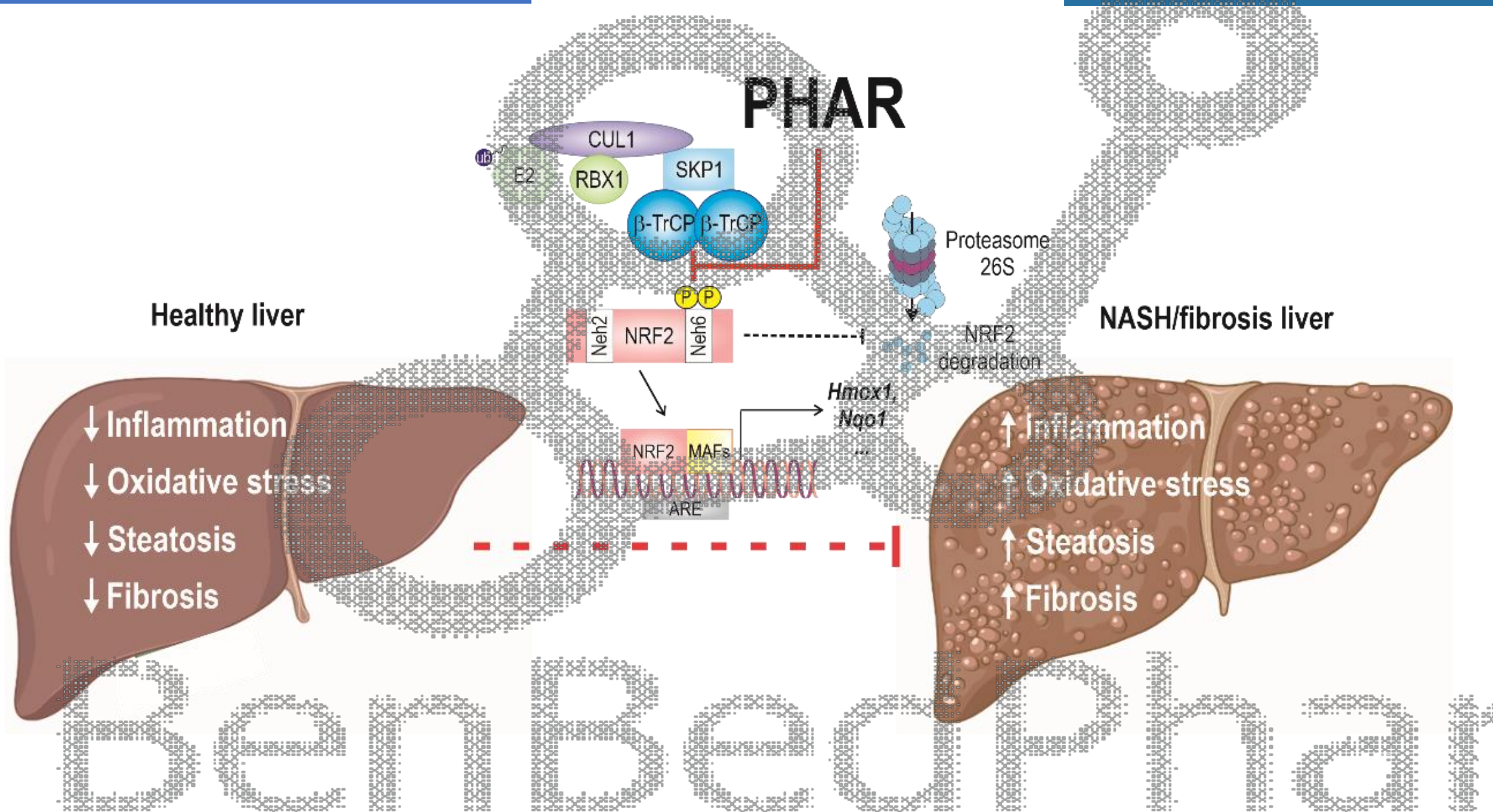


STAM model of liver degeneration

STZ + high fat diet



Summary



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Thank you

Cuadrado's lab:



Dr. Ana Isabel Rojo Sanchís
Dr. Ángel Juan García Yagüe
Dr. Maribel Escoll Guerrero

José Jiménez Villegas
Daniel Carnicero Senabre
Eduardo Cazalla Ibáñez

Dr. Raquel Fernández Ginés

