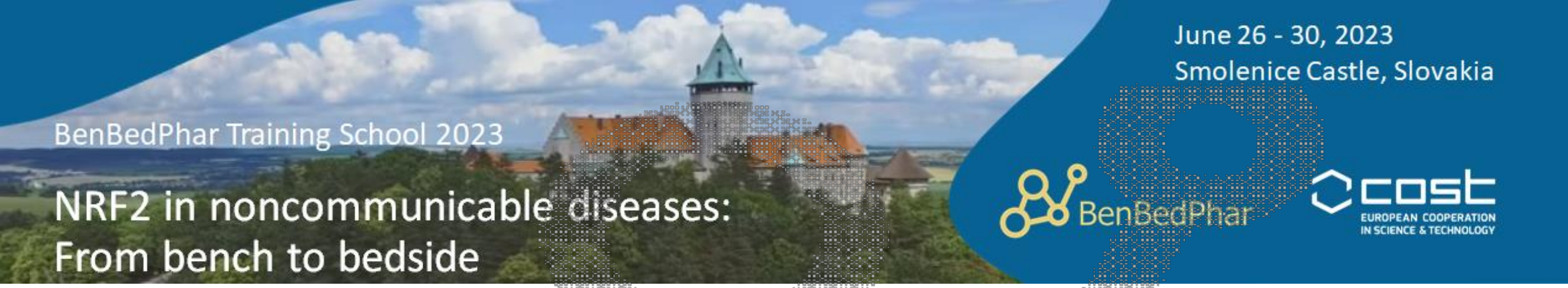
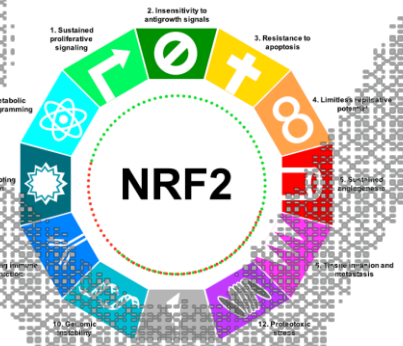


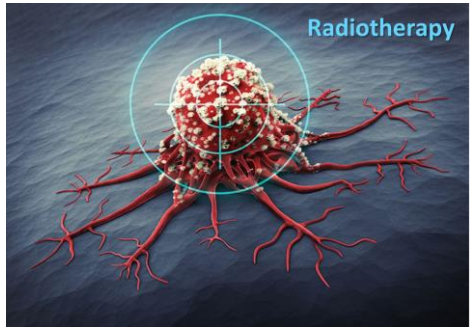
NRF2 in cancer and radiotherapy

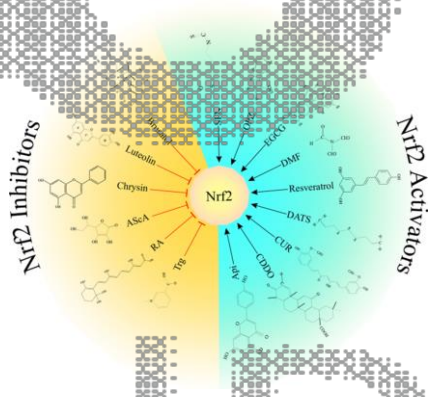
Dr. Gina Manda
"Victor Babeș" National Institute of Pathology

Outline

- The NRF2 status in solid tumors
- Tumor cells in the beat of the radiotherapy rifle
- NRF2 inhibitors in radiotherapy

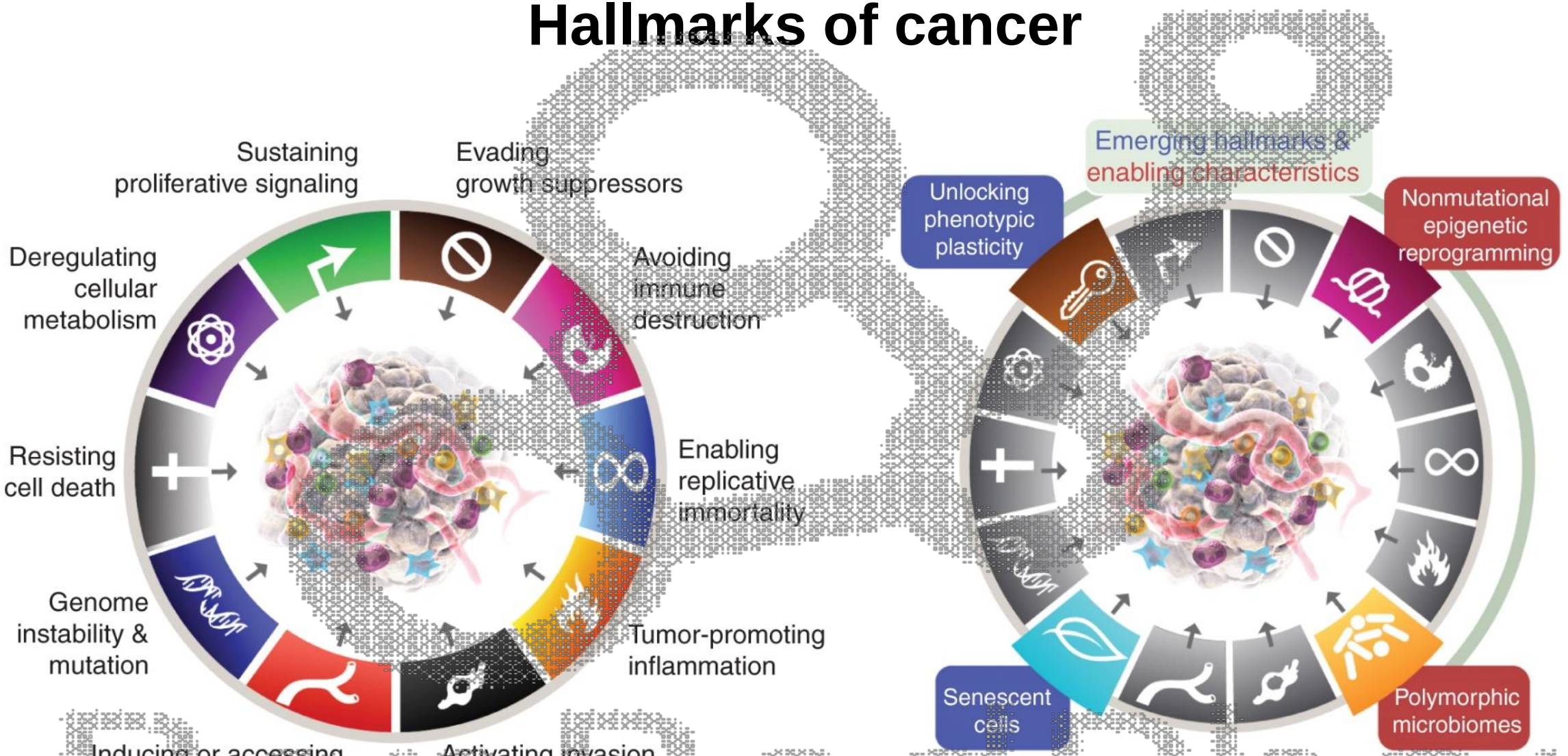






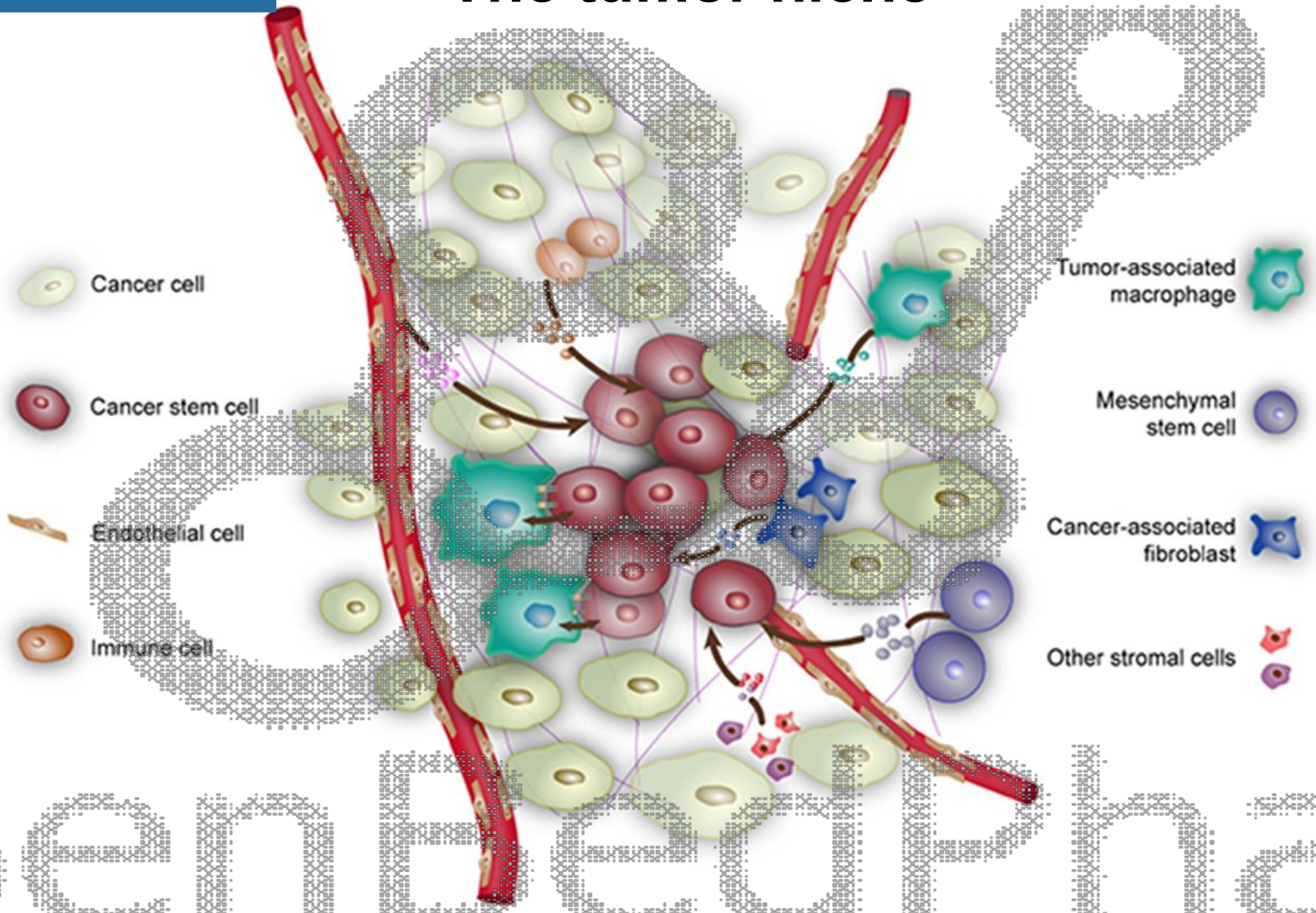
I. The NRF2 status in solid tumors

Hallmarks of cancer



Hanahan D. Cancer Discov. 2022; 12(1):31-46.

The tumor niche

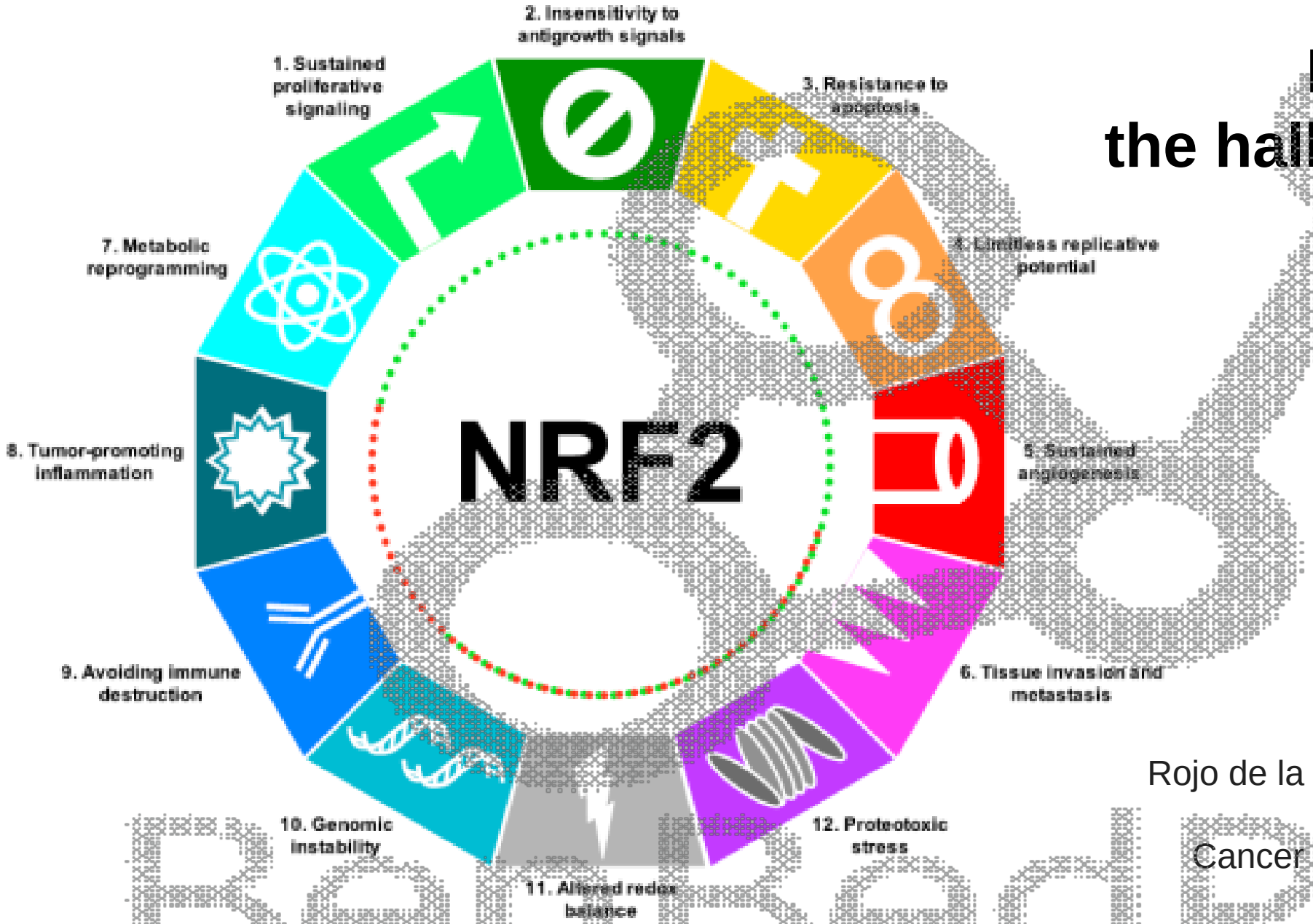


He J et al, Oncotarget. 2018; 9: 1326-1345.

Addiction of tumor cells to NRF2

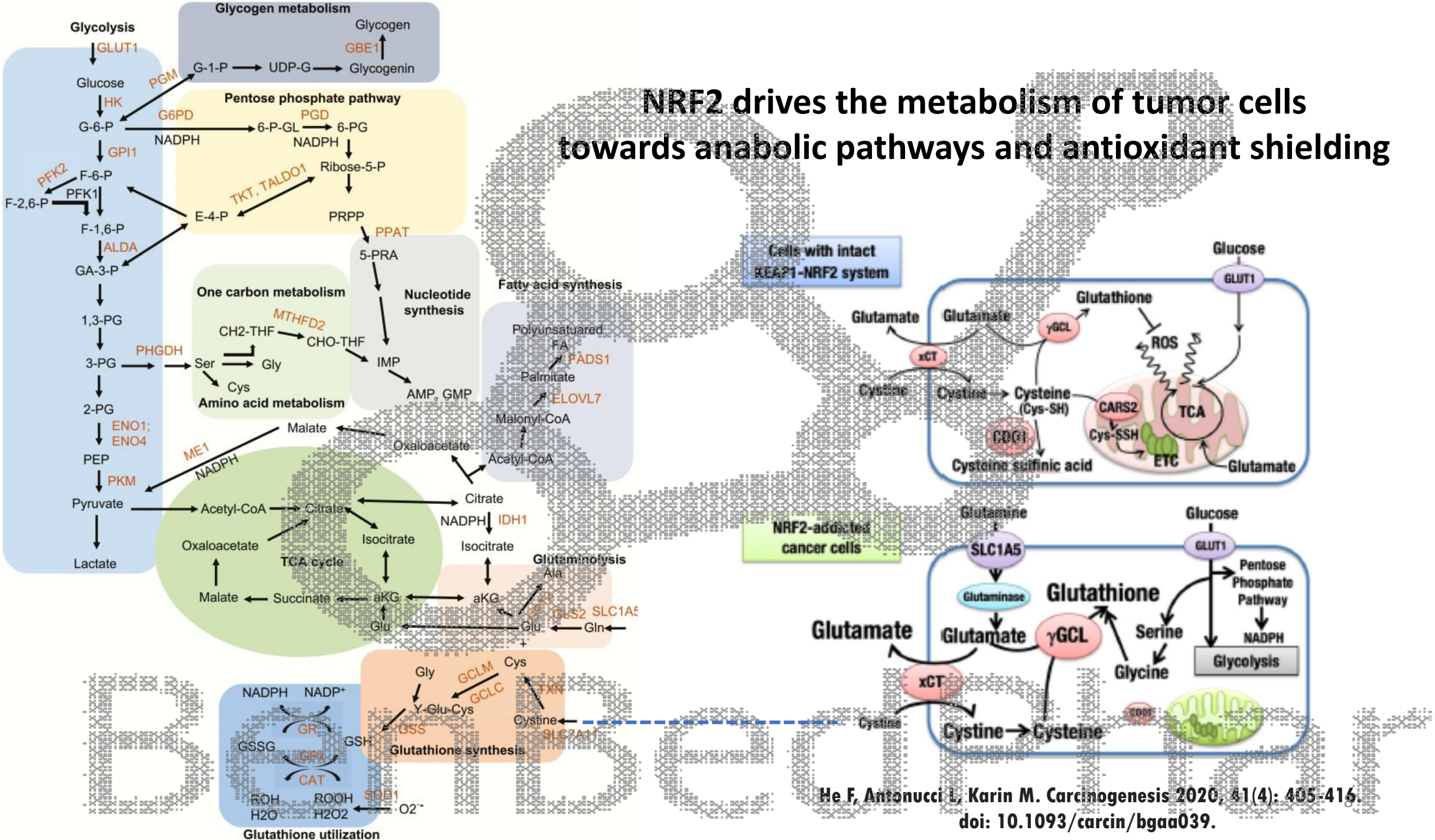
- **Survival and proliferation advantage**
- **Resistance to therapy**

NRF2 and the hallmarks of cancer



Rojo de la Vega M, Chapman E, Zhang DD.
Cancer Cell. 2018, 9;34(1): 21-43.

NRF2 drives the metabolism of tumor cells towards anabolic pathways and antioxidant shielding

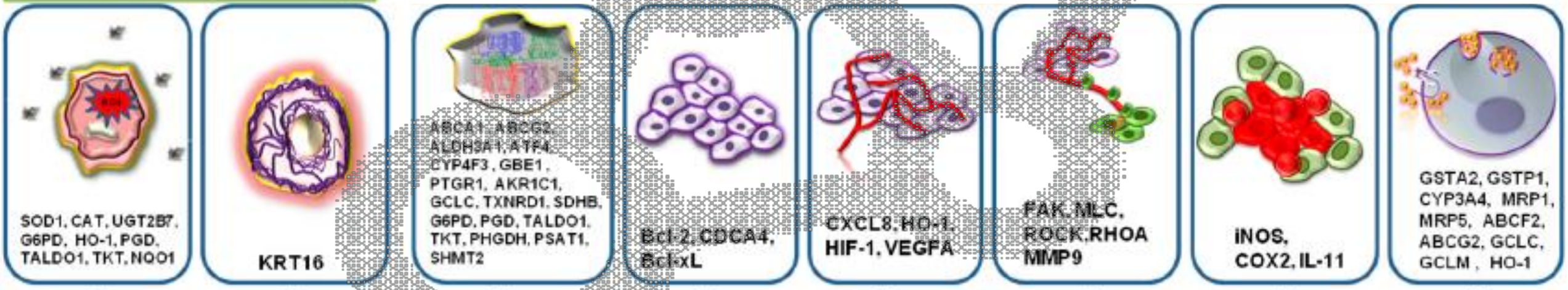


He F, Antonucci L, Karin M. Carcinogenesis 2020, 41(4): 405-416. doi: 10.1093/carcin/bgaa039.

The dual role of NRF2 in cancer

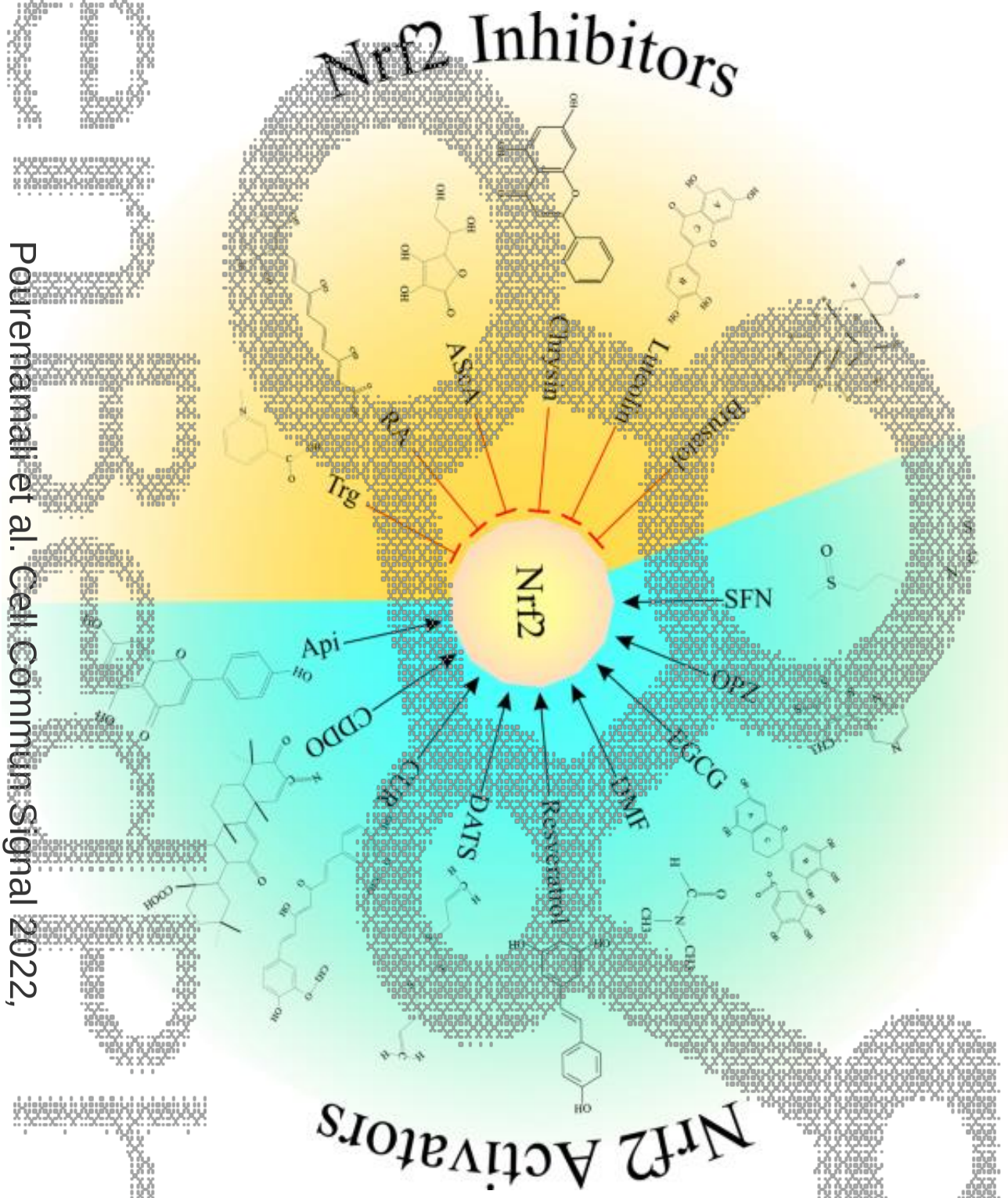
Anti-carcinogenic activity

Pro-carcinogenic activity



Zimta AA et al. Cancers (Basel) 2019,

Cancer therapy

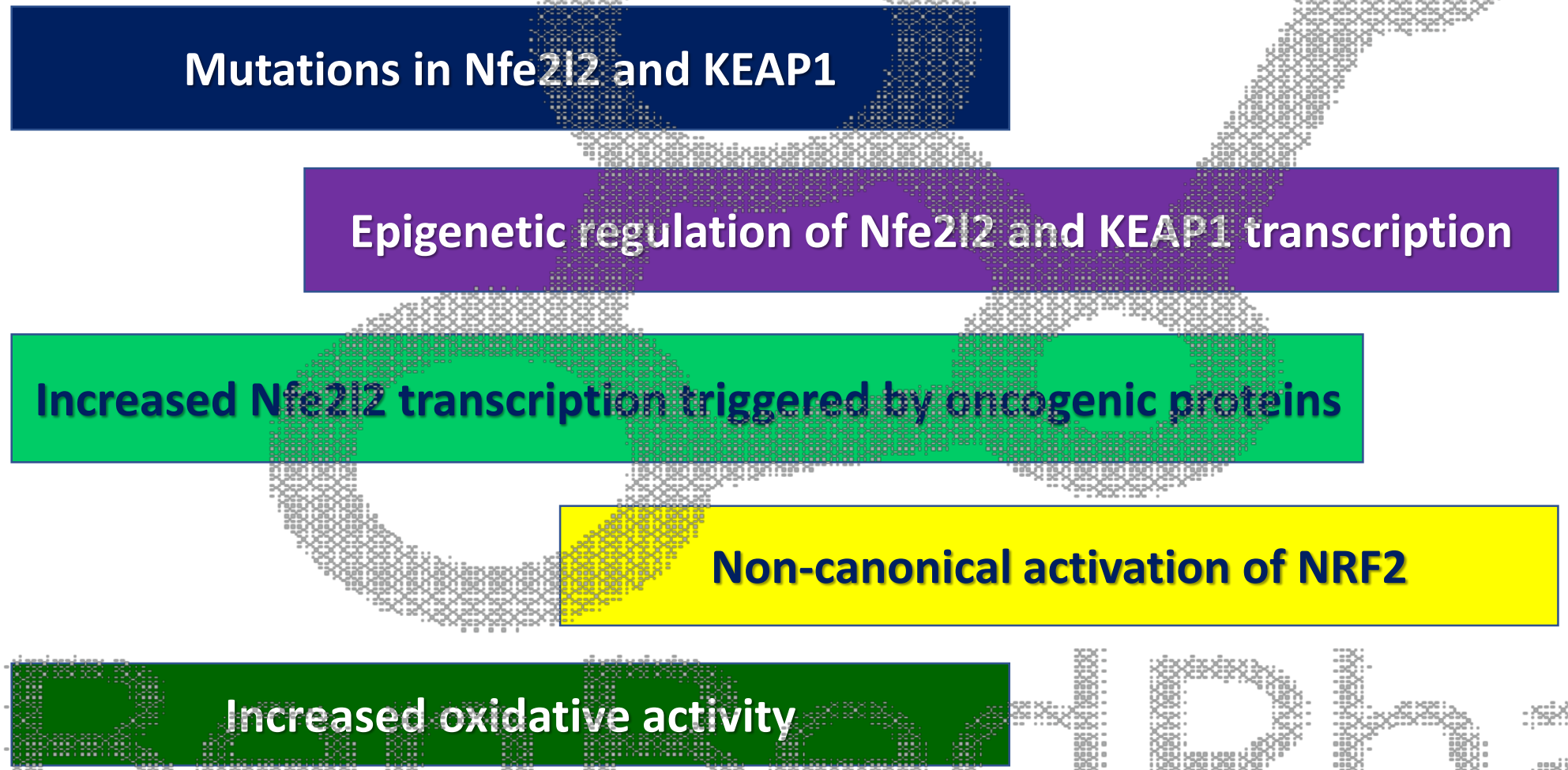


Cancer prevention

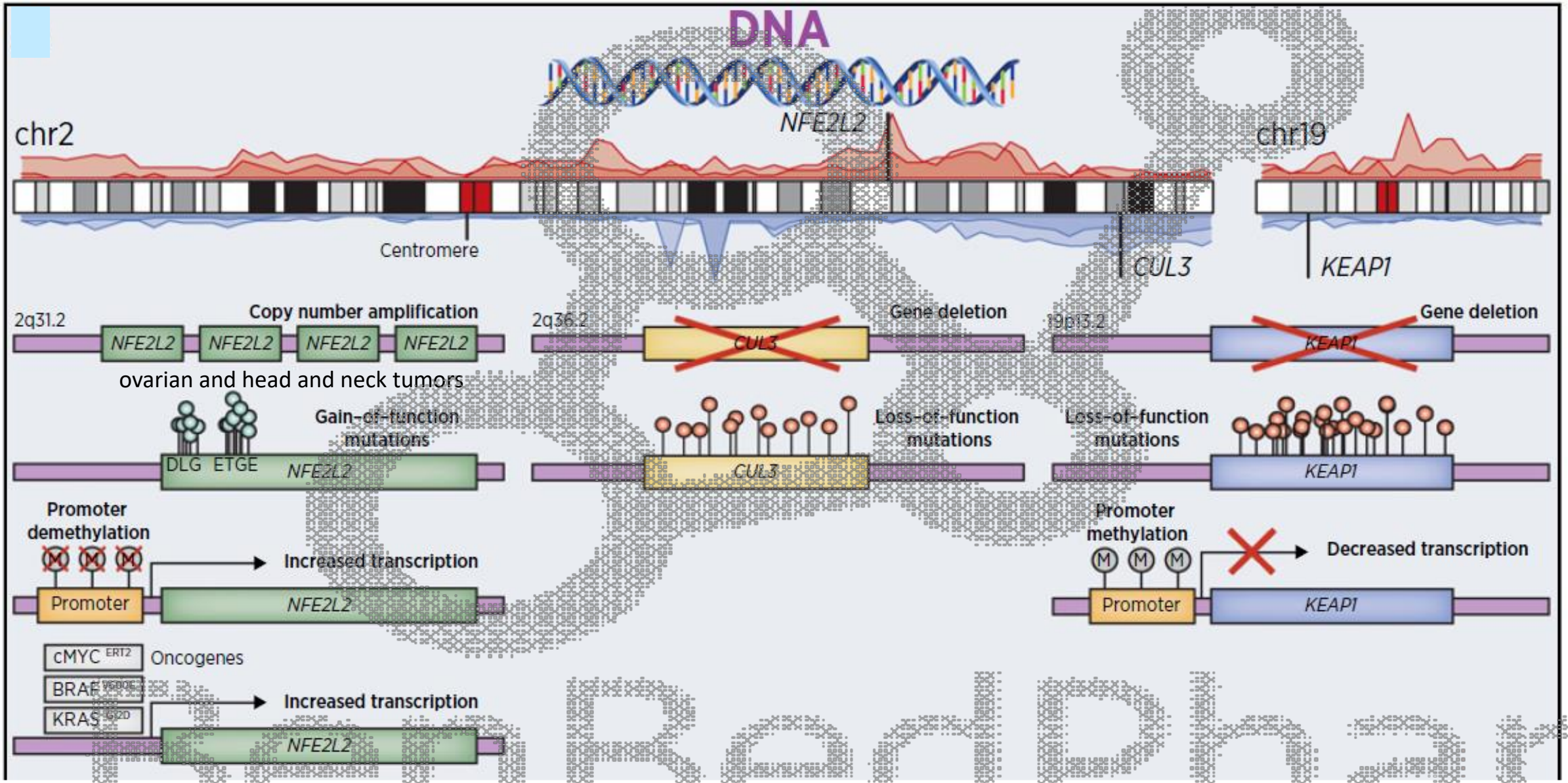
Pouremamali et al. Cell Commun Signal 2022, 20: 100

Increased NRF2 levels and transcriptional activity in types of tumors

Poor survival of cancer patients with NRF2-addicted tumors

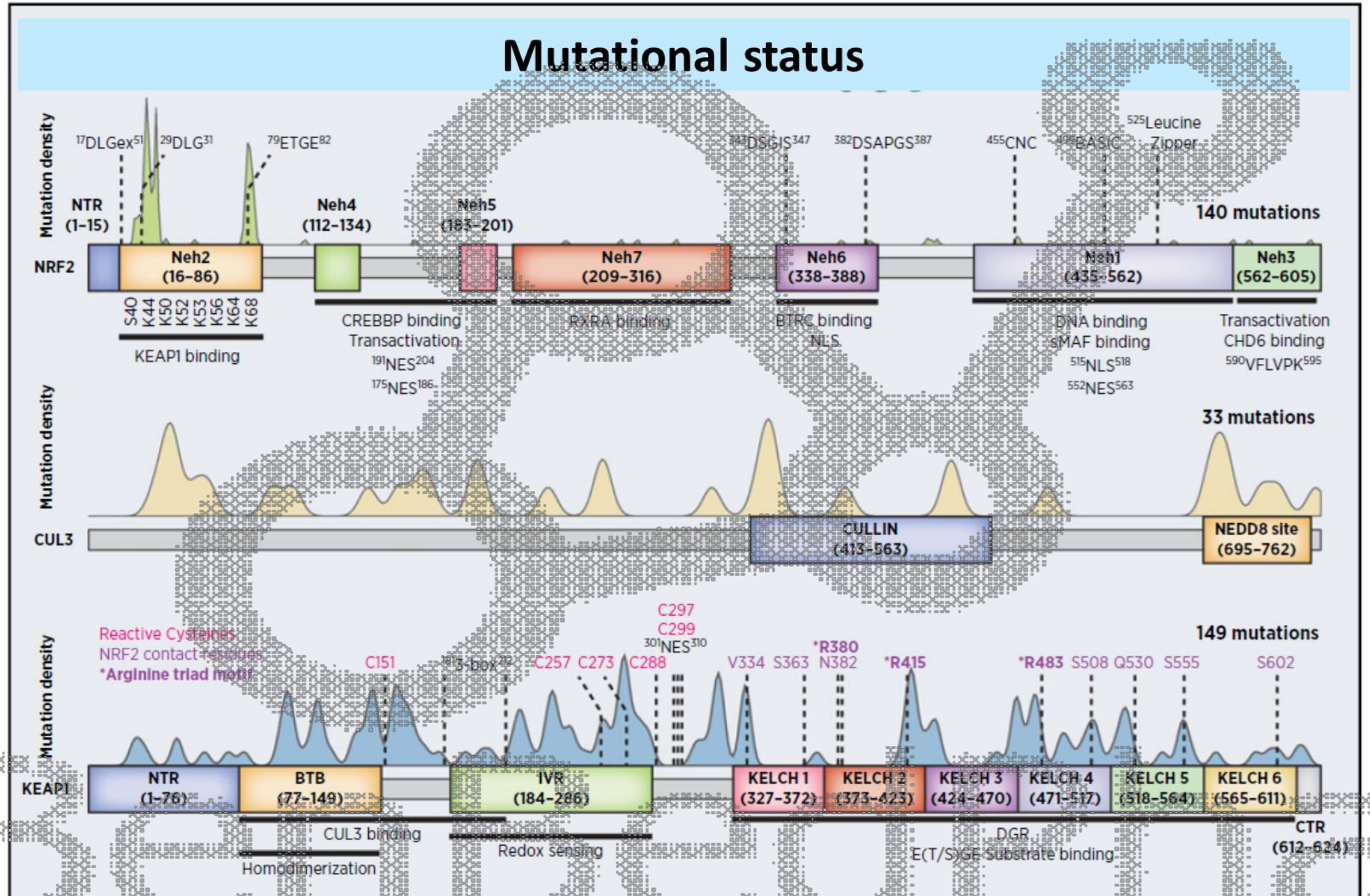


Cloer EW et al. NRF2 Activation in Cancer: From DNA to Protein. Cancer Res. 2019, 79(5): 889-898.



Cloer EW et al. NRF2 Activation in Cancer: From DNA to Protein. Cancer Res. 2019, 79(5): 889-898

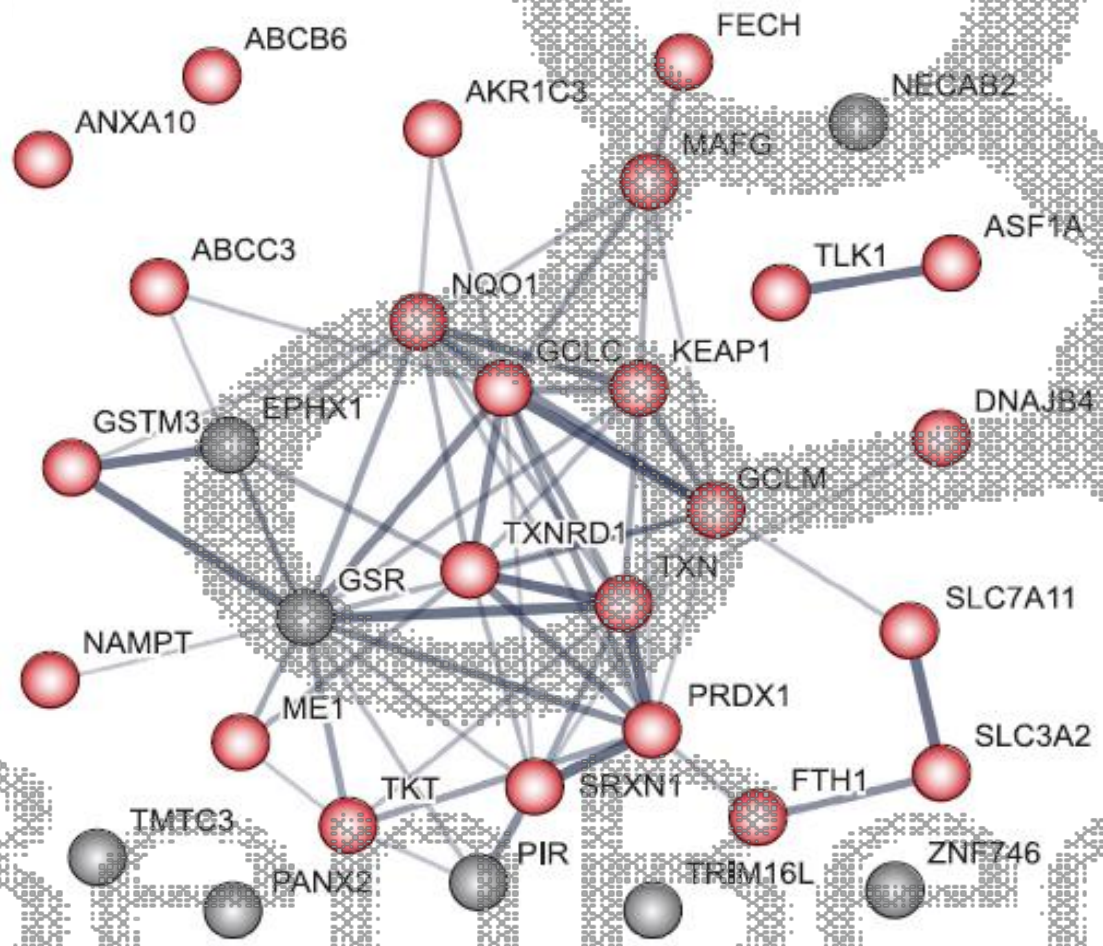
Mutational status

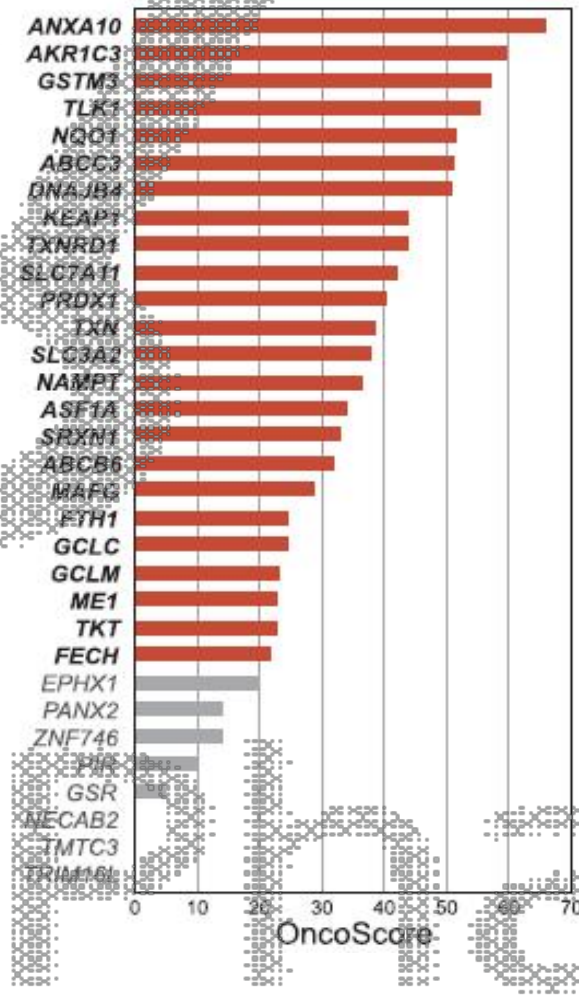


Cloer EW et al. NRF2 Activation in Cancer: From DNA to Protein. Cancer Res. 2019, 79(5): 889-898.

The Cancer Genome Atlas (TCGA) consortium

32 NRF2 target genes are consistently upregulated in 9000 TCGA tumor samples with Nfe2l2 mutations (lung, uterine/endometrial, bladder, head and neck cancer)





Levings DC et al. Redox Biol. 2018, 19: 235-249.

The Cancer Genome Atlas Programme (TCGA)

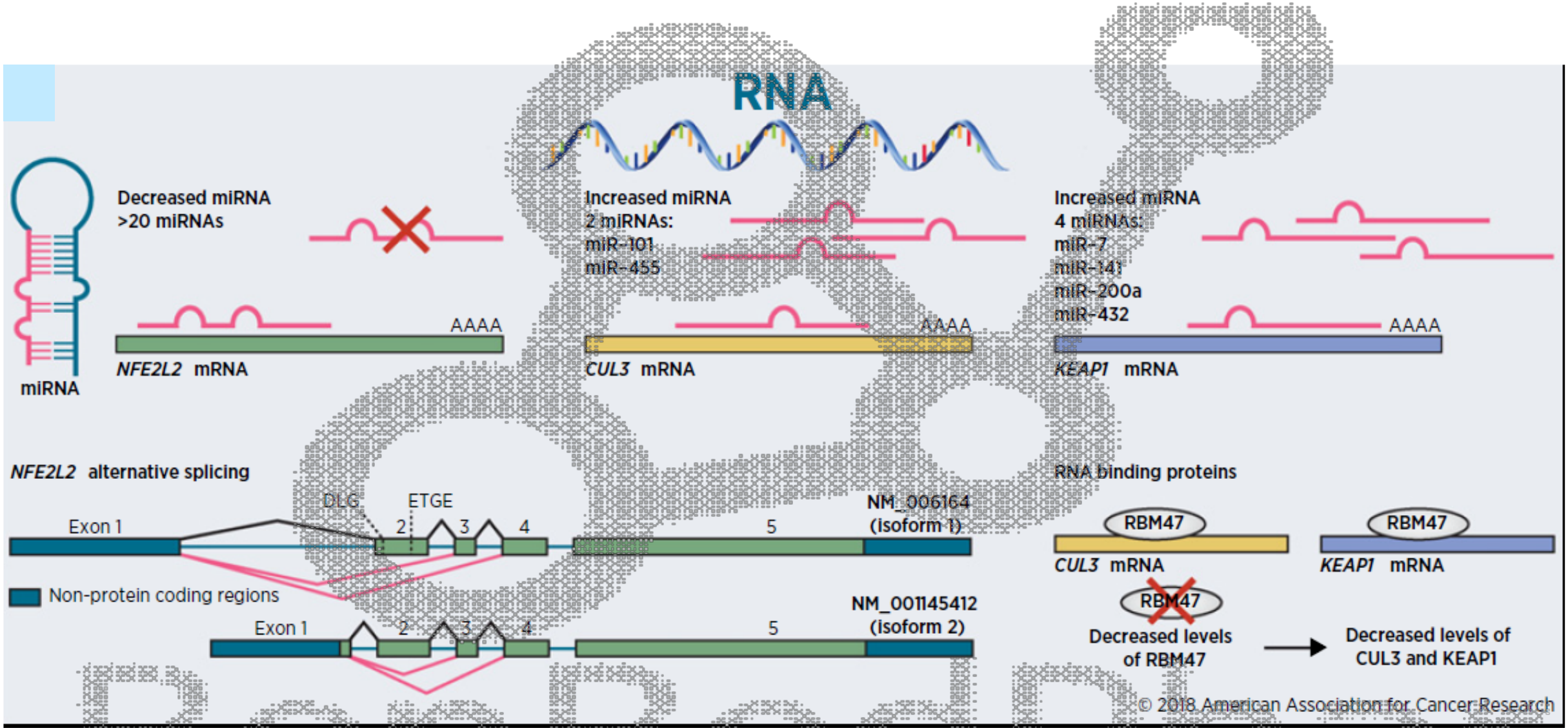
Metanalysis on 226 TCGA studies reported genetic mutations and copy number alterations in the KEA1-NRF2 signaling system in carcinomas

- Lung carcinoma: LUSC (31.4%) and LUAD (24%)
- Uterine carcinoma: 20.6%
- Head and neck carcinoma: 17.4%
- Esophageal carcinoma: 19.8%
- Bladder carcinoma: 14.8%

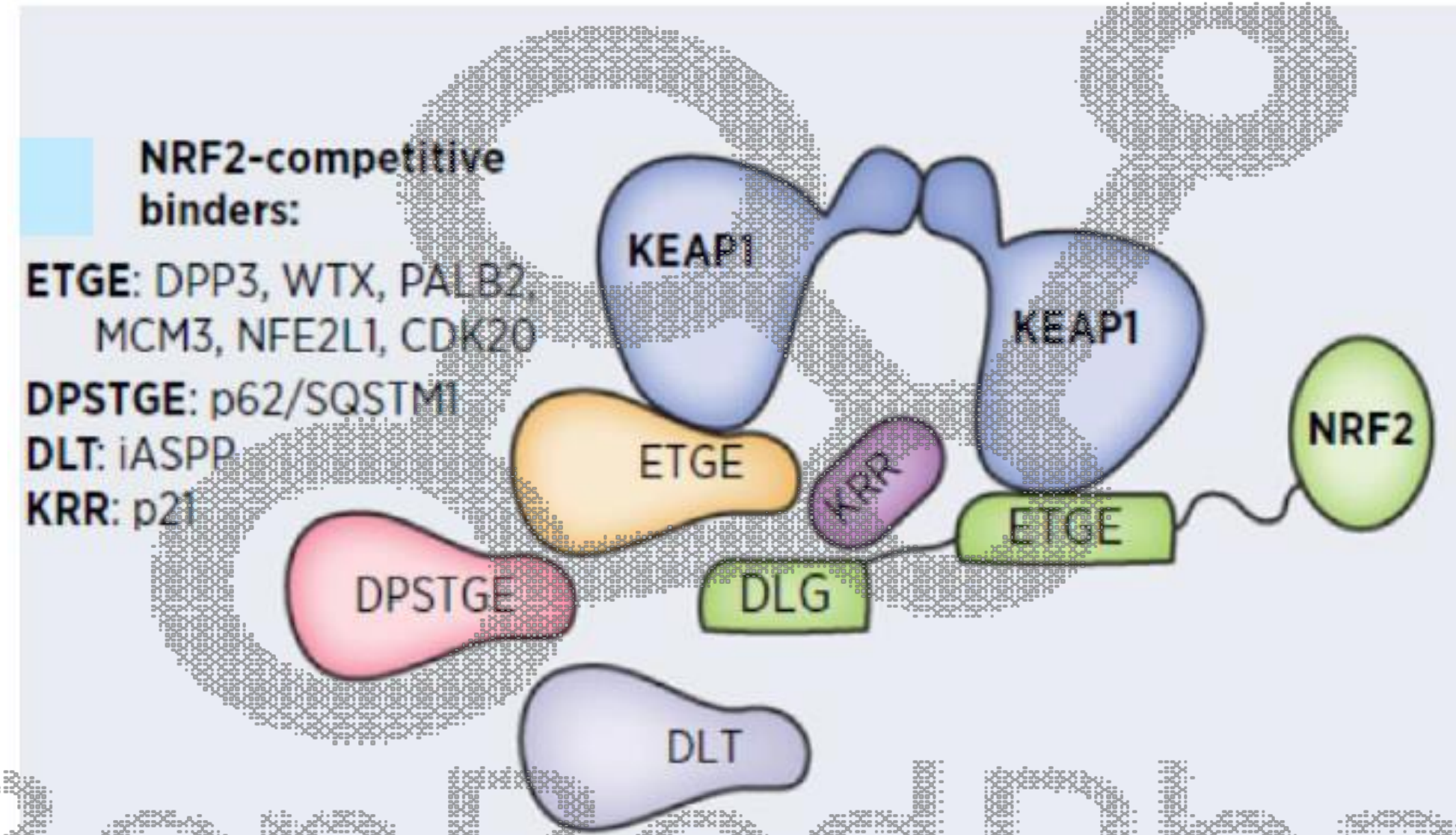
Mutational rates of Nfe2l2 underrepresent the true number of NRF2 hyperactive tumors

American Cancer Society. Cancer facts & figures 2018.

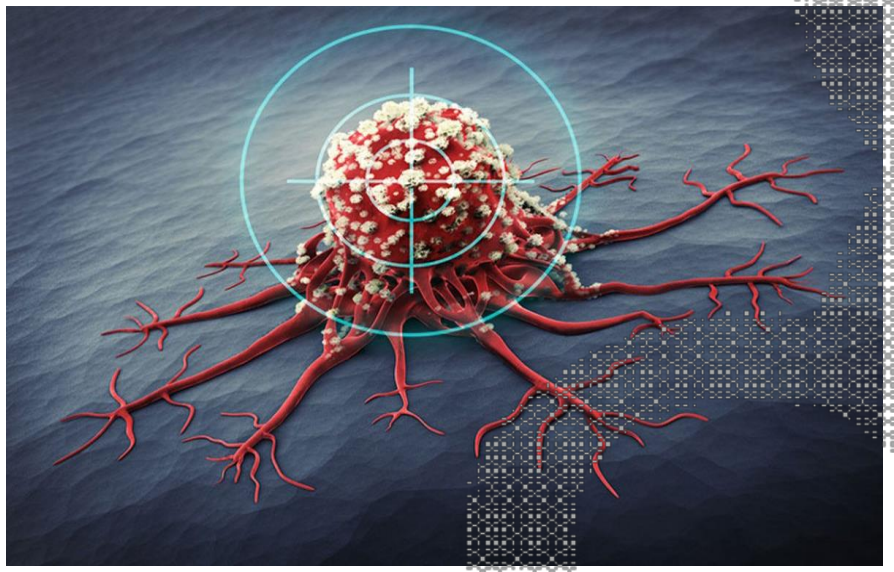
Nongenomic mechanisms of NRF2 activation



Cloer EW et al. NRF2 Activation in Cancer: From DNA to Protein. Cancer Res. 2019, 79(5): 889-898.



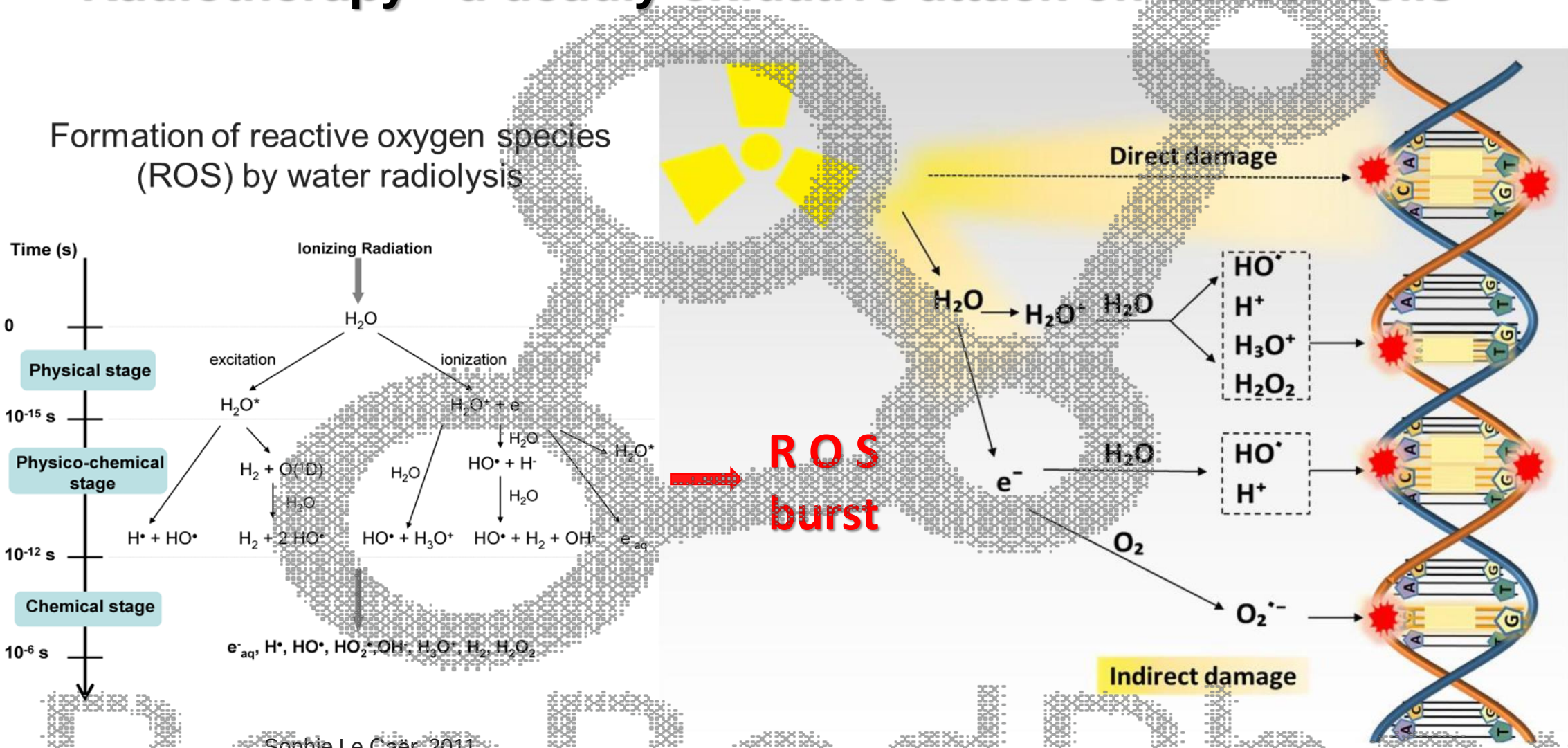
Cloer EW et al. NRF2 Activation in Cancer: From DNA to Protein. Cancer Res. 2019, 79(5): 889-898.



II. NRF2 in tumor cells in the beat of the radiotherapy rifle

https://www.the-scientist.com/news/cancer-cells-go-incognito-to-cause-therapy-relapse-70157

Radiotherapy - a deadly oxidative attack on cancer cells

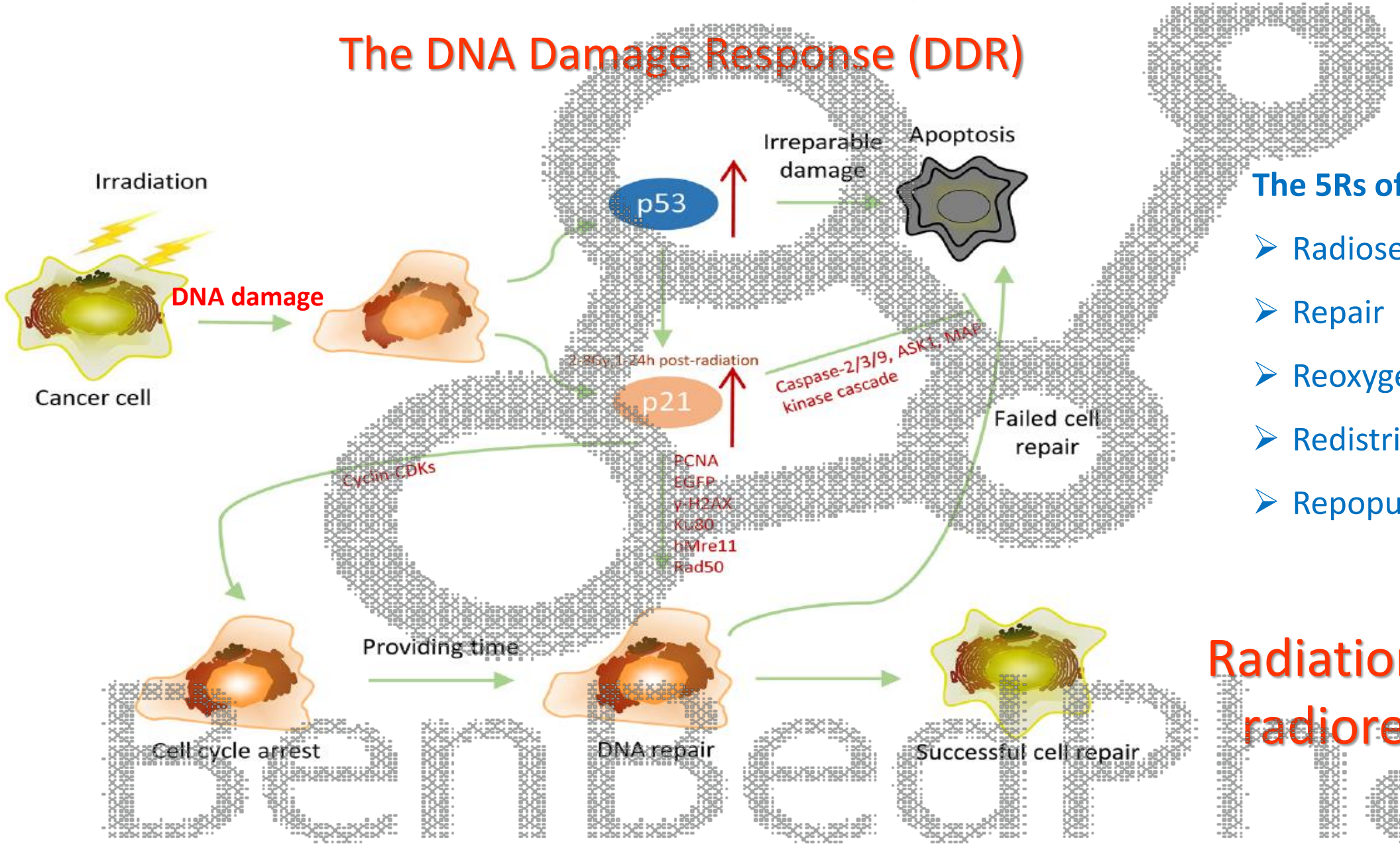


Sophie Le Caër, 2011

Desideratum: tumor cell death

A decision of life or death is taken by irradiated cells

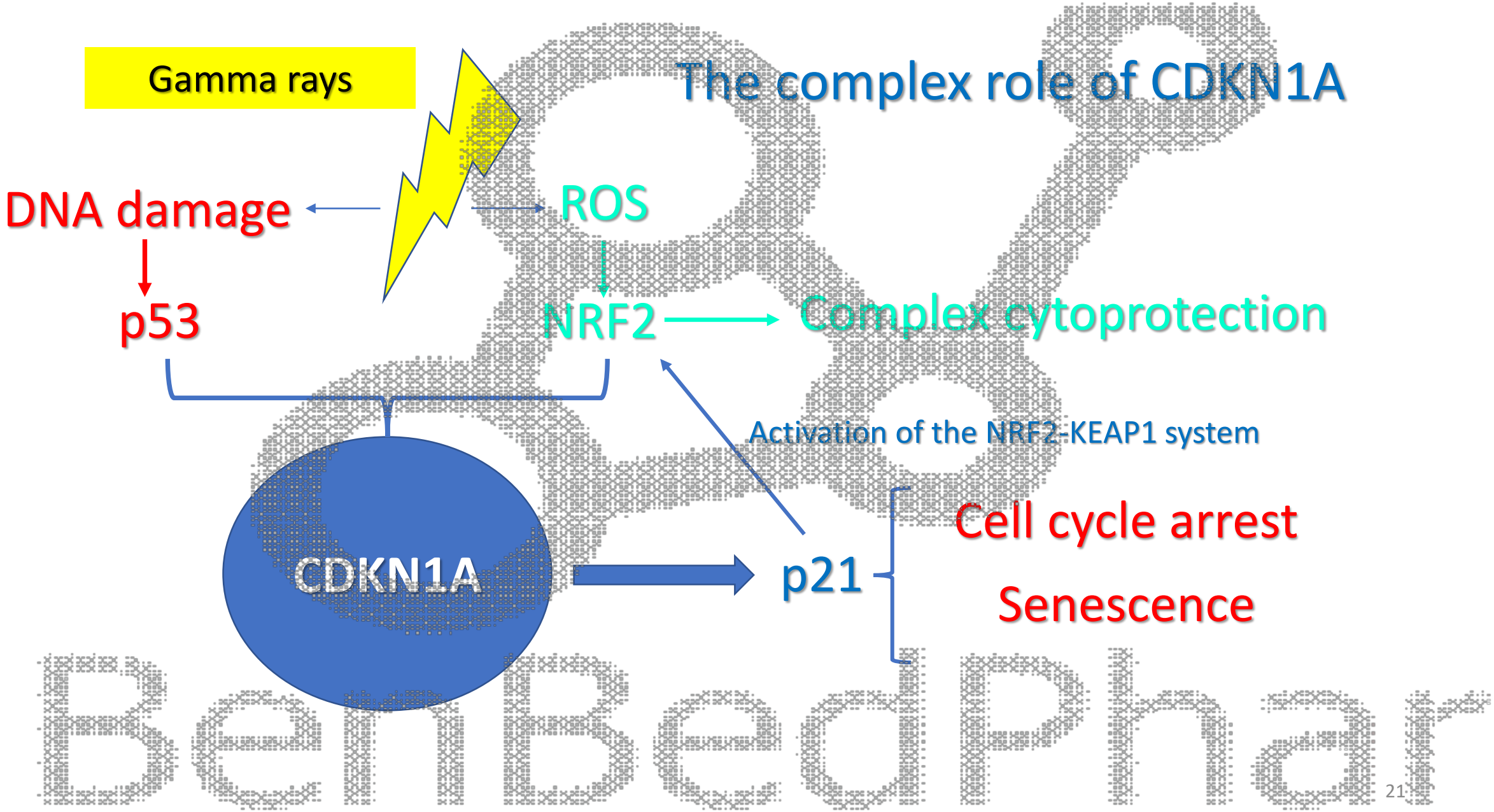
The DNA Damage Response (DDR)



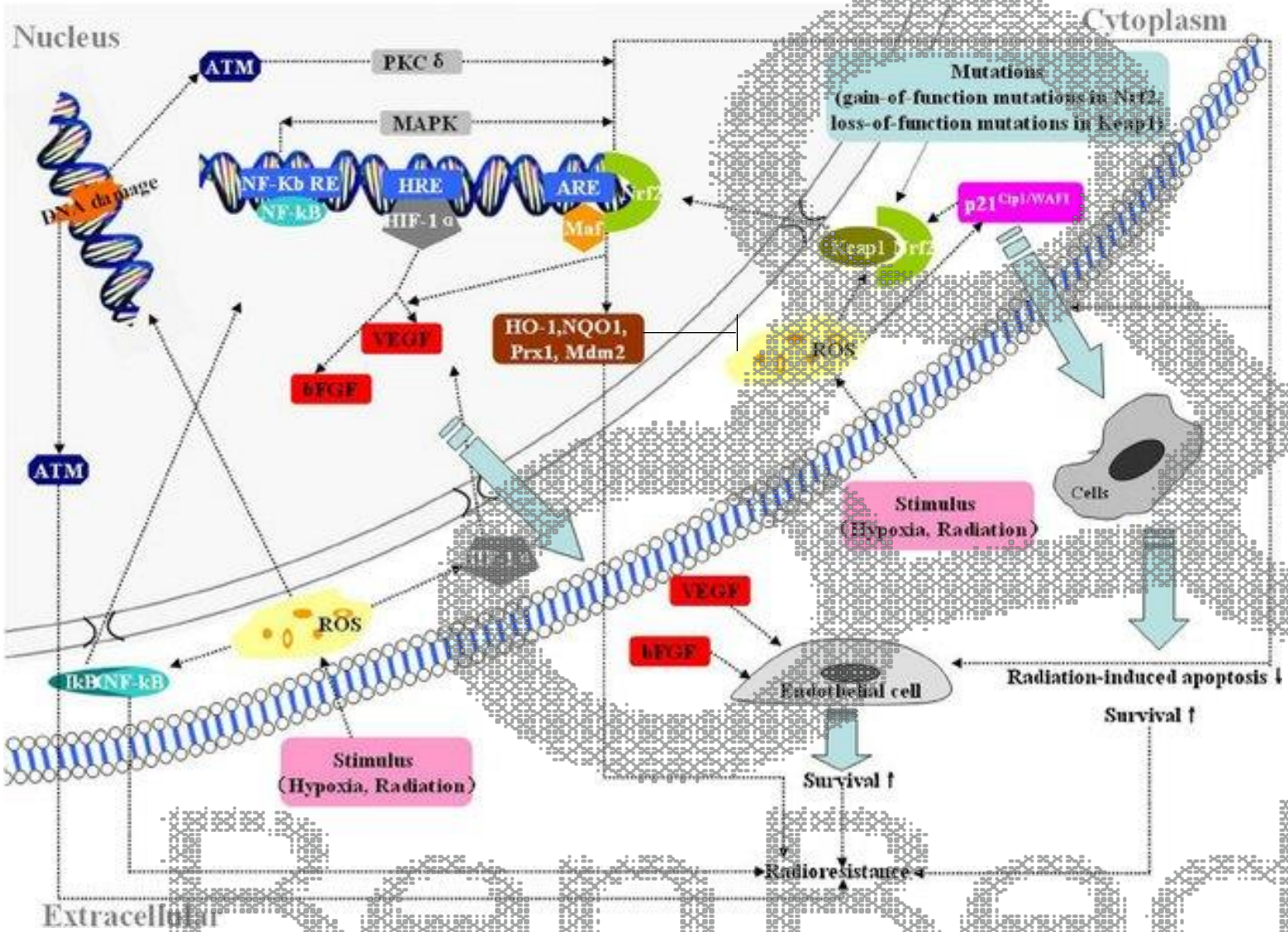
The 5Rs of Radiobiology

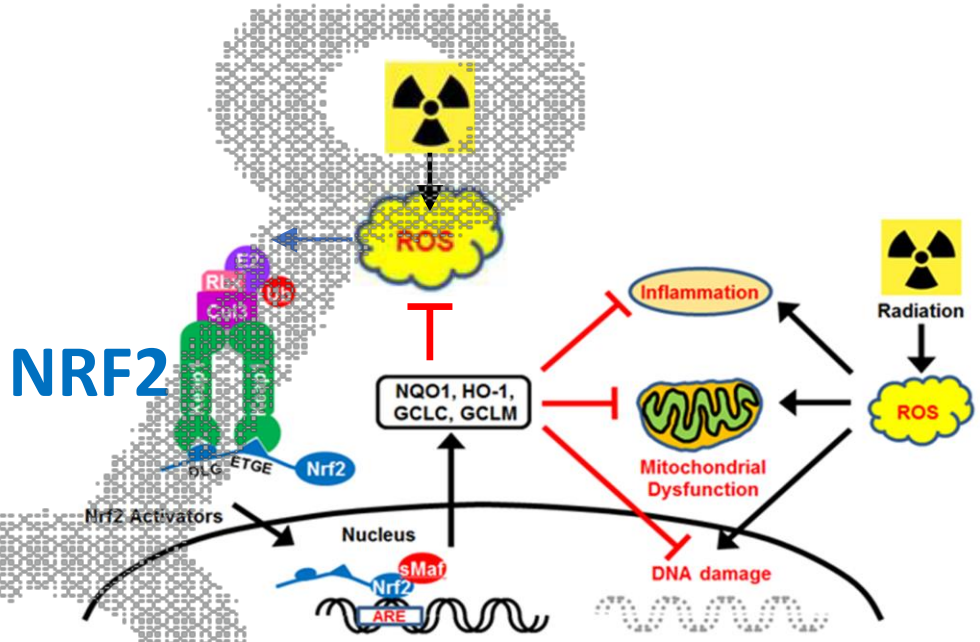
- Radiosensitivity
- Repair
- Reoxygenation
- Redistribution
- Repopulation

Radiation-induced radioresistance


Gamma rays
The complex role of CDKN1A
DNA damage
ROS
p53
NRF2
Complex cytoprotection
Activation of the NRF2-KEAP1 system
CDKN1A
p21
Cell cycle arrest
Senescence

A concert of transcription factors shape radiation–induced resistance of tumor cells





Nakagami Y. J Rare Dis Res Treat. (2017) 2(3): 11-15

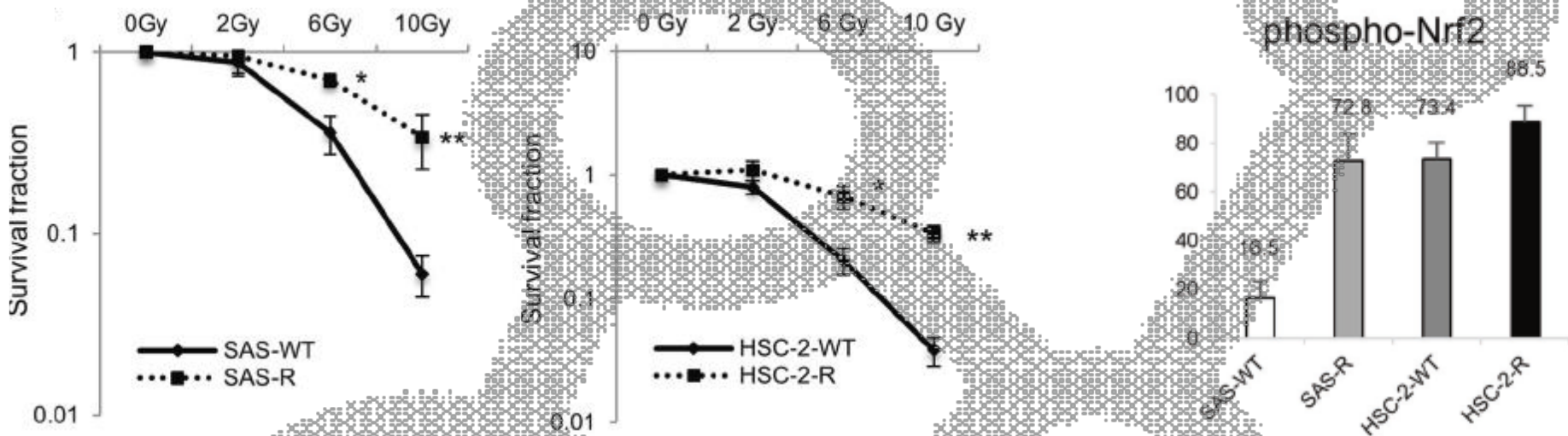
Increased survival of irradiated cells and acquired radioresistance in successive irradiation sessions

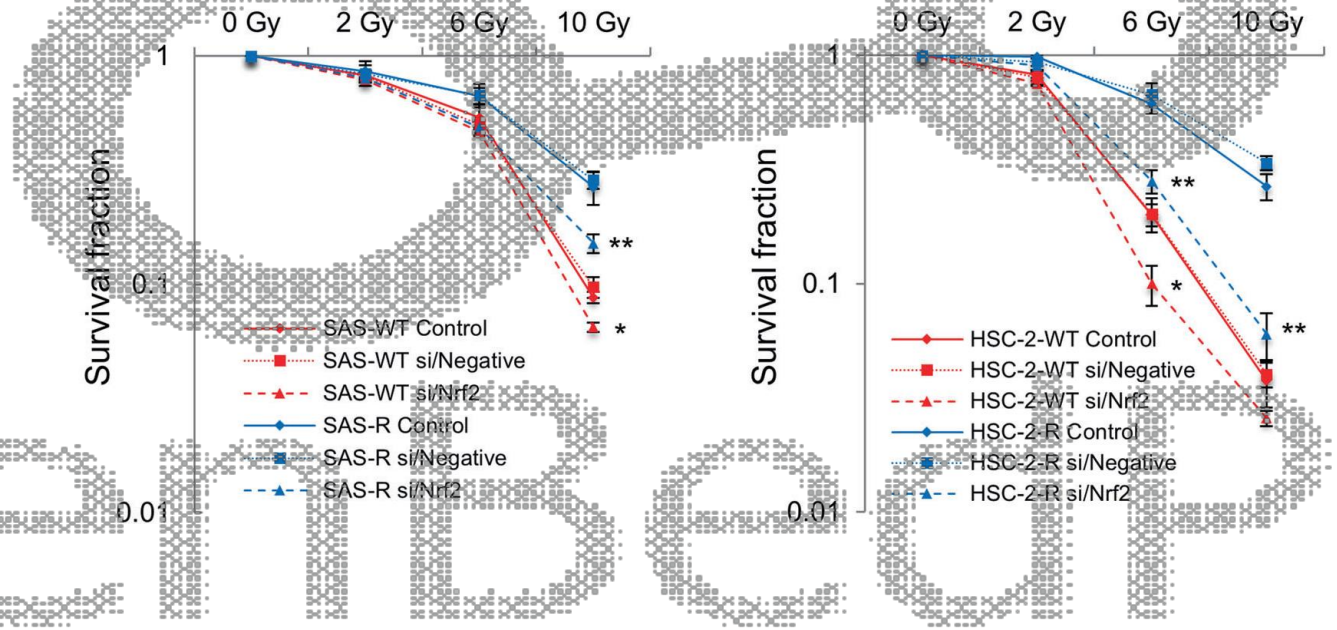
Zhou S et al. Nrf2 is a potential therapeutic target in radioresistance in human cancer. Crit Rev Oncol Hematol.

Radioresistant *versus* wild-type tumor cells

In vitro study on cell lines relevant for oral squamous carcinoma

- SAS cells (with a functional TP53 mutation and lower basal levels of p-NRF2)
- HSC-2 cells (with a non-functional TP53 mutation and higher basal levels of p-NRF2)

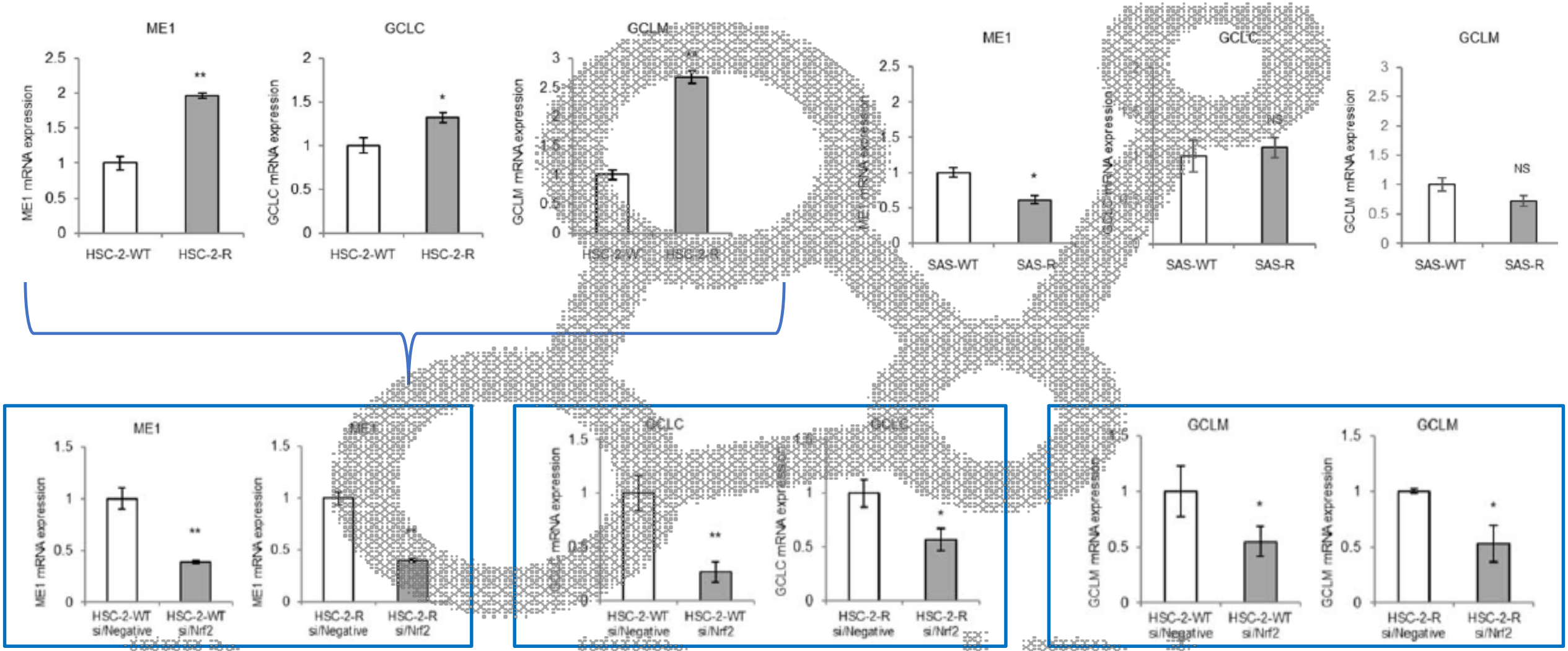




Matsuoka Y et al.
Lab Invest. 2022,
102(8):896-907

HSC: cell line bearing a TP53 non-functional mutation

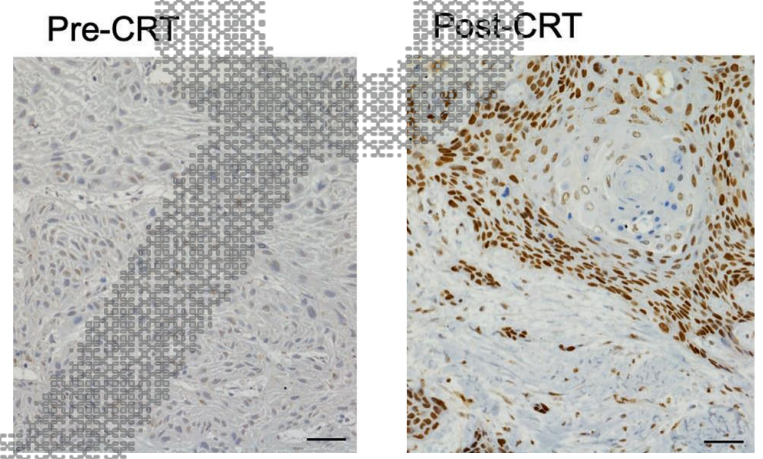
SAS: cell line bearing a functional TP53 mutation

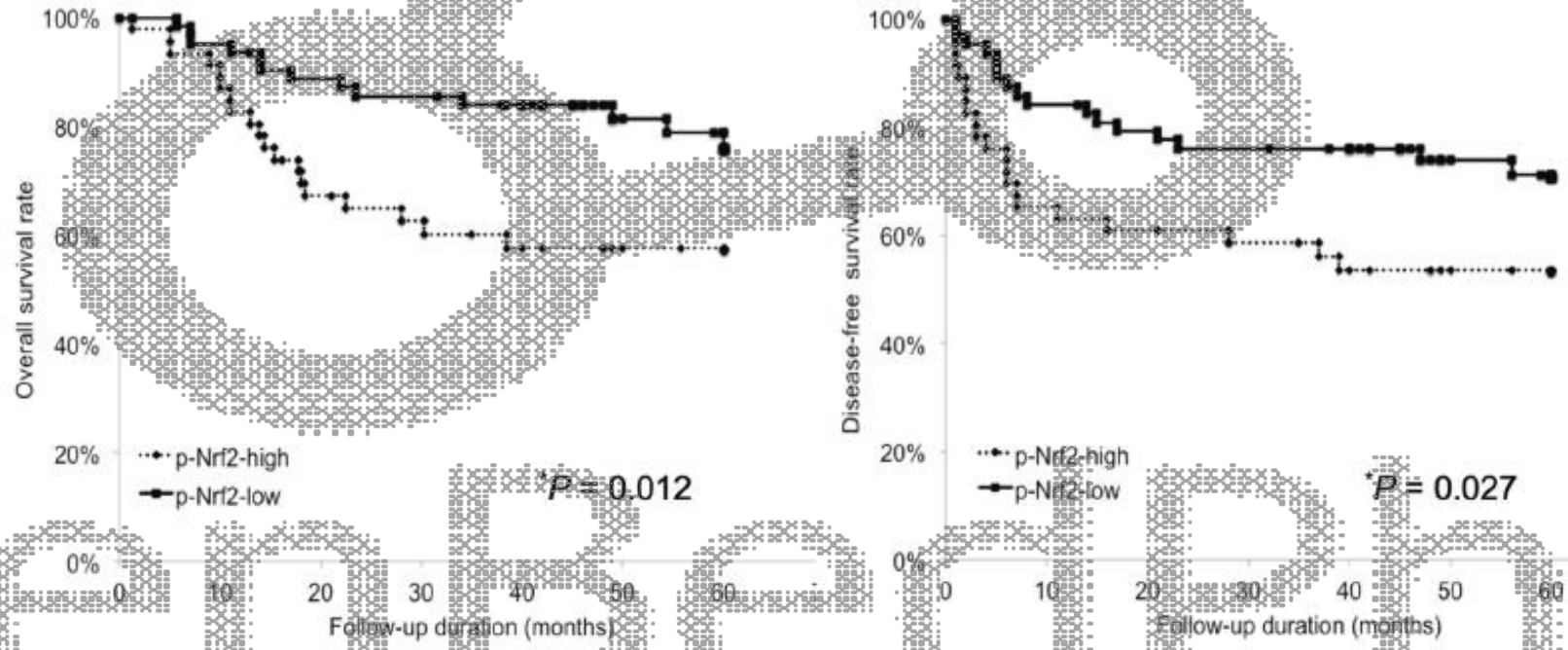


Irradiation-induced NRF2 and radioresistance

110 patients with oral squamous cell carcinoma subjected to preoperative chemoradiotherapy (CRT)

- 64 patients (58.2%) had low levels of p-NRF2 post-CRT
- 46 patients (41.8%) had high levels of p-NRF2-post-CRT

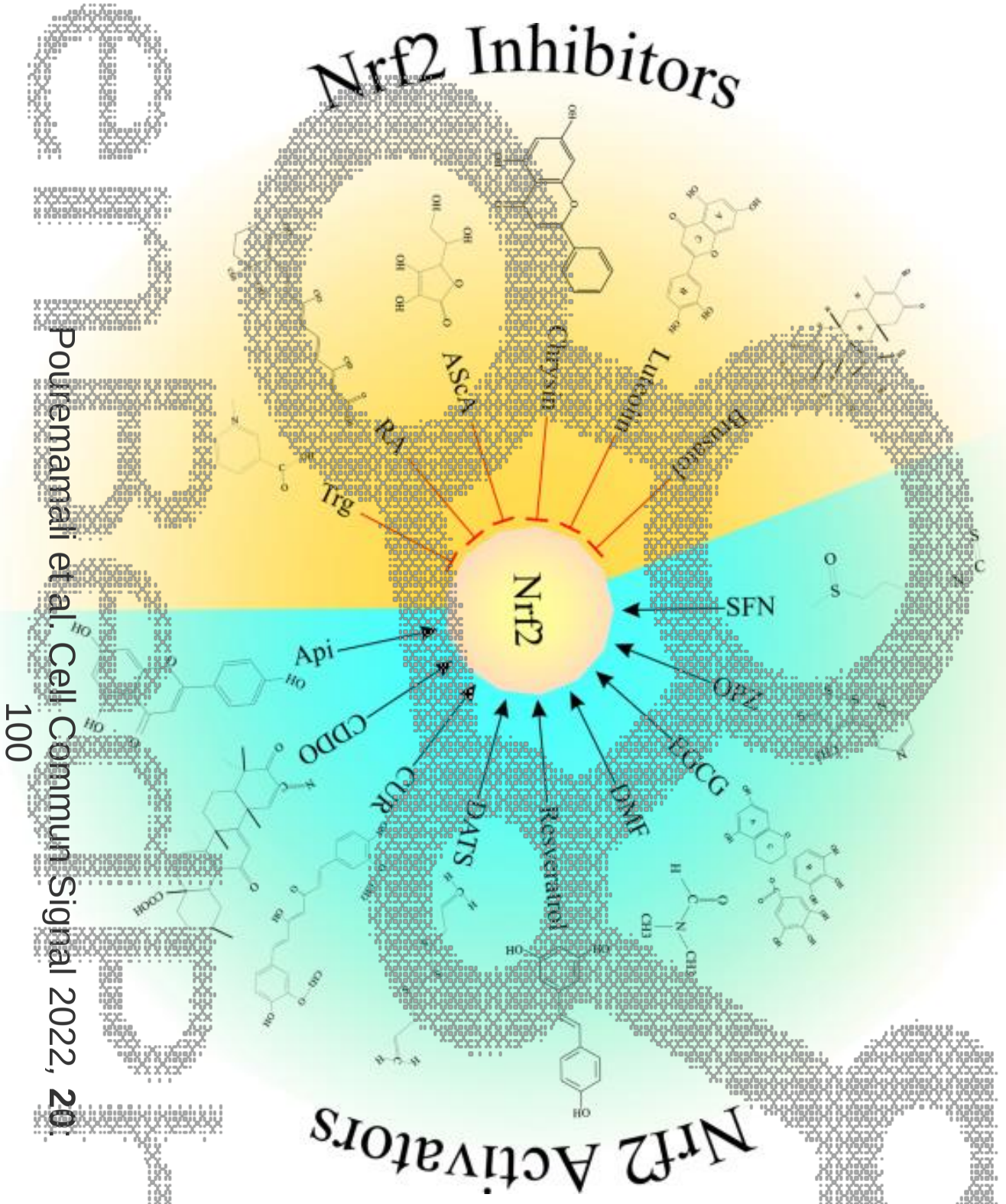




Matsuoka Y et al. Lab Invest. 2022; 102(8):896-907

III. NRF2 inhibitors in radiotherapy

Overcoming radioresistane



Protection against radiation-induced skin damages

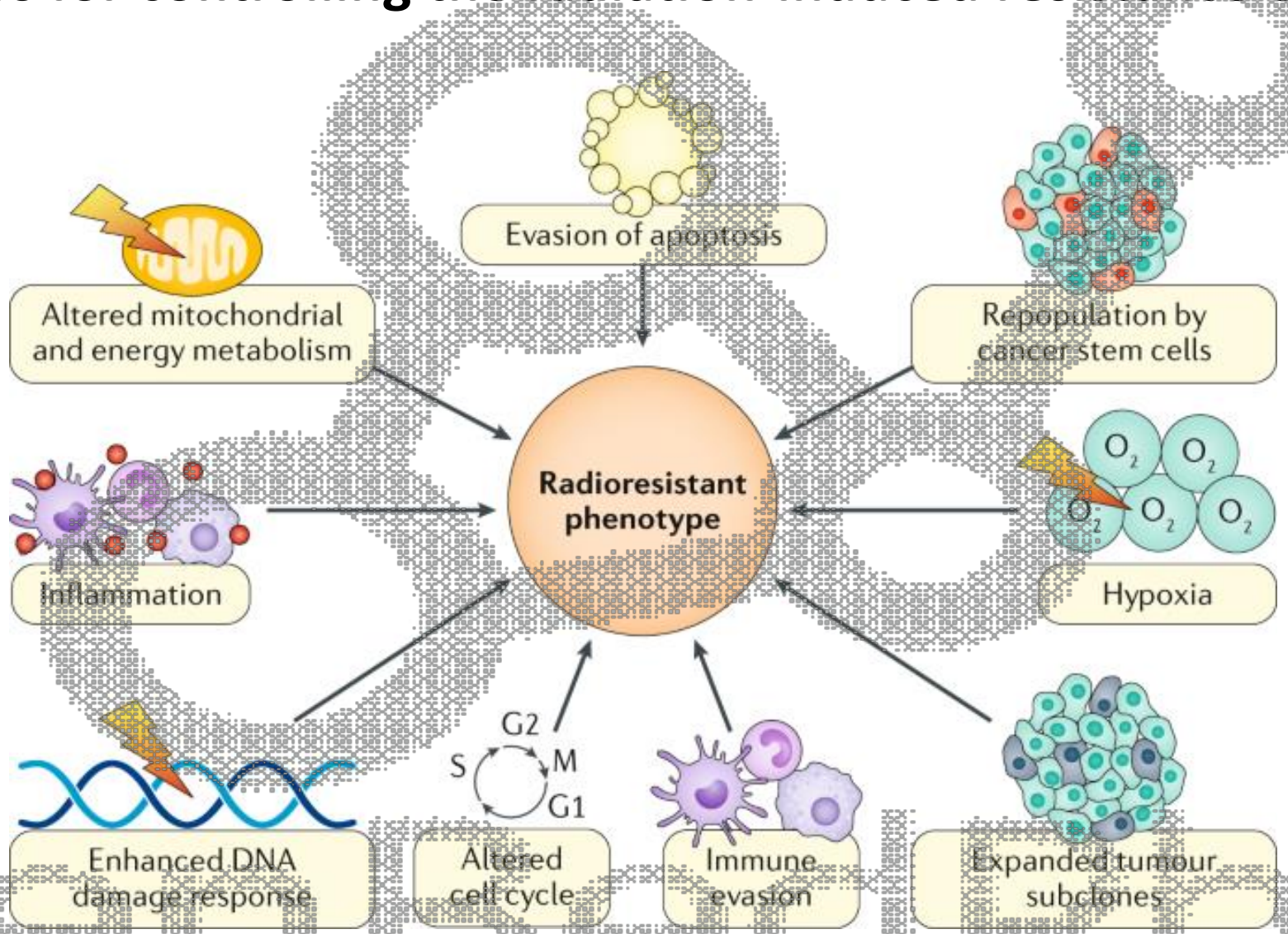
Pouremamali et al. Cell Commun Signal 2022, 20:100

NRF2 inhibitors

Brusatol	Triterpene lactone compound	Stimulation of Nrf2 poly-ubiquitination
Luteolin	Plant flavone	NRF mRNA degradation, Reduction of Nrf2 binding to AREs
Trigonelin	Coffee-derived alkaloid	Prevention of nuclear translocation of NRF2
Ascorbic acid	Natural vitamin	Electrophilic modification of Keap1-Cys-151
Retinoic acid	Metabolite of vitamin A	Prevention of nuclear translocation of NRF2
Chrysin	Plant flavone	Prevention of nuclear translocation of NRF2

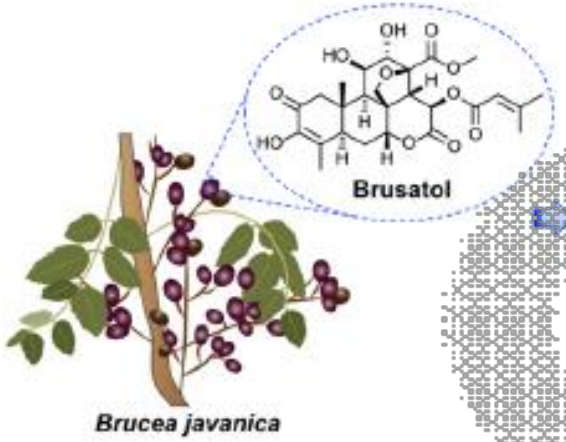
Pouremamali F et al. Cell Commun Signal. 2022, 20(1):100. doi: 10.1186/s12964-022-00906-3.

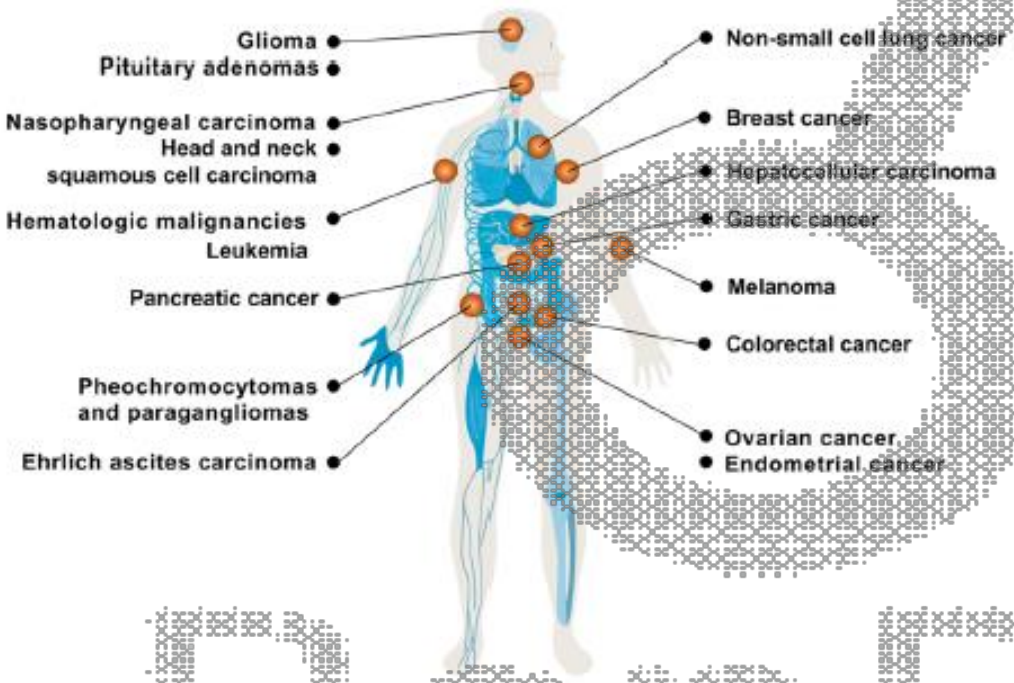
NRF2 inhibitors for controlling the radiation-induced resistance of tumor cells



Buckley AM et al. Nat Rev Gastroenterol Hepatol. 2020 May;17(5):298-313. doi: 10.1038/s41575-019-0247-2.

Brusatol co-treatment for overcoming radioresistance





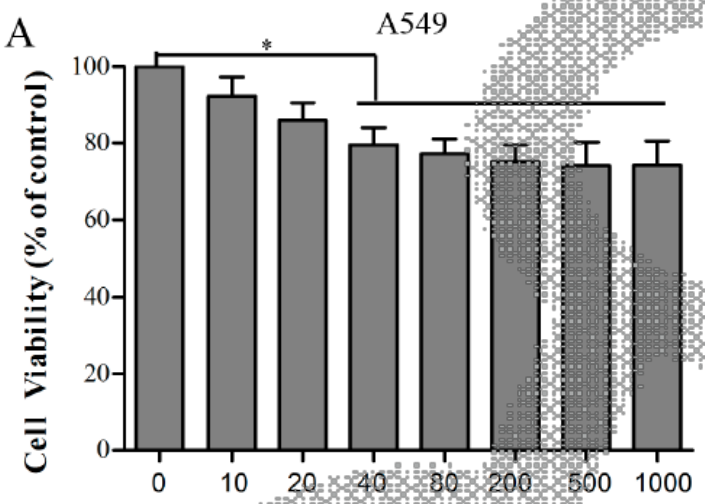
At nanomolar concentrations,
brusatol inhibits at post-translational levels
short-lived proteins like NRF2 and stress proteins that
account for radiation-induced radioresistance

Anti-cancer activity of brusatol

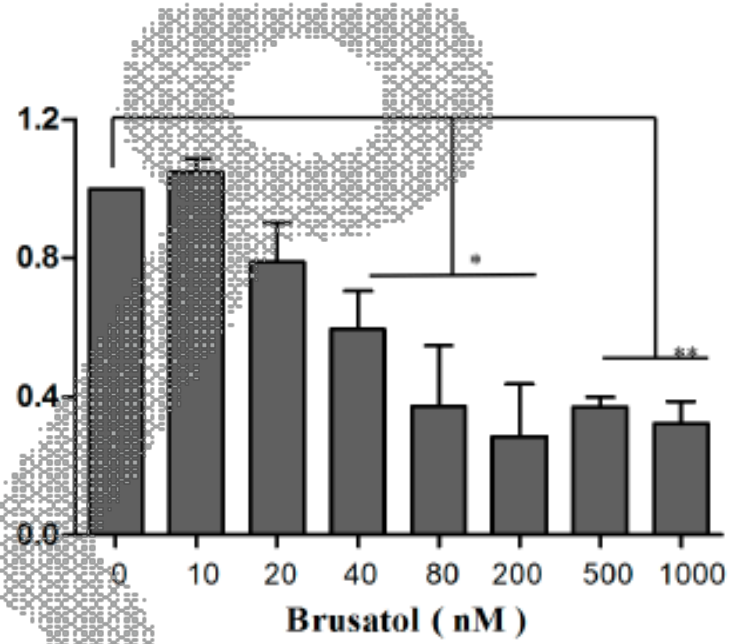
He T et al. Biomed Pharmacother. 2023, 158:114134.
Yang Y et al. Oxid Med Cell Longev. 2020, 2020:9867595.
Cai SJ et al. Cell Biosci. 2019, 9: 45.
Harder B et al. Mol Carcinog. 2017, 56(5):1493-1500.
Vartanian S et al. Mol Cell Proteomics. 2016, 15(4): 1220-1231.
Ren D et al. Proc Natl Acad Sci U S A. 2011, 108(4): 1433-1438.

Human A549 non-small cell lung cancer cells with high levels of NRF2

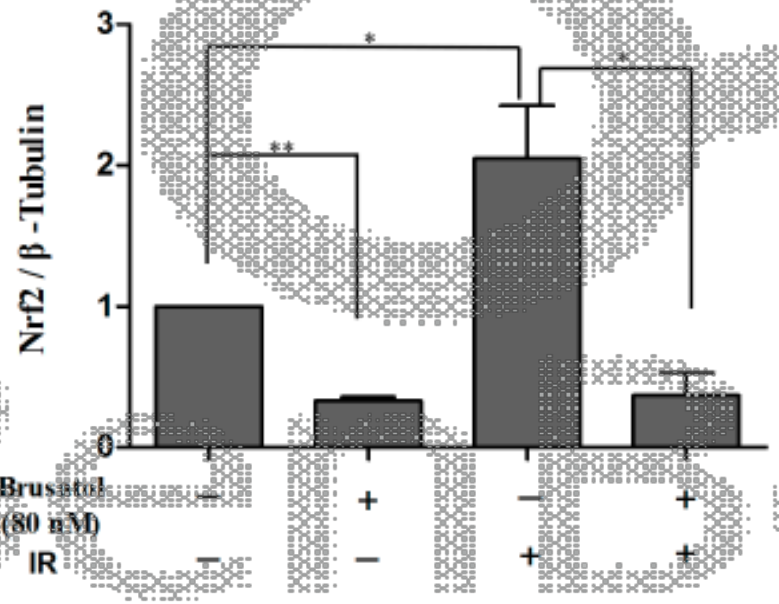
Evaluation at 24 h



Evaluation at 6 h



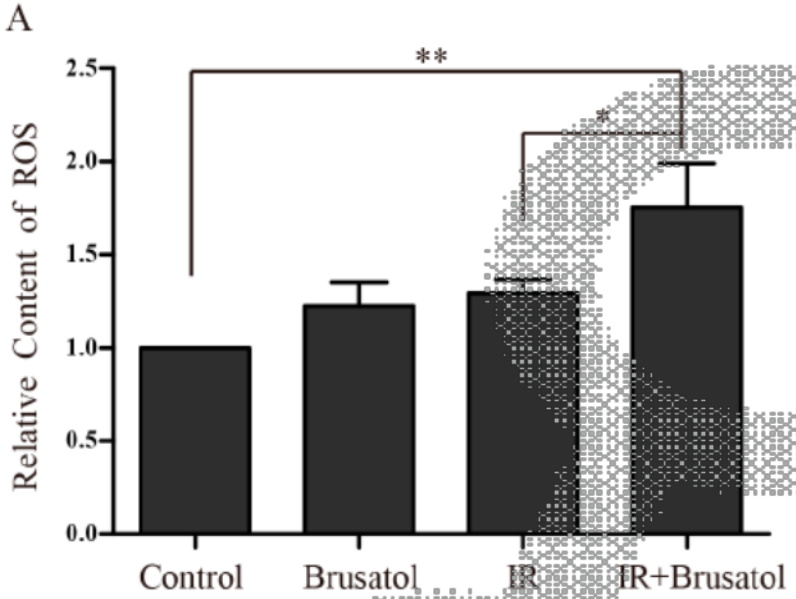
Evaluation at 2 h post-irradiation



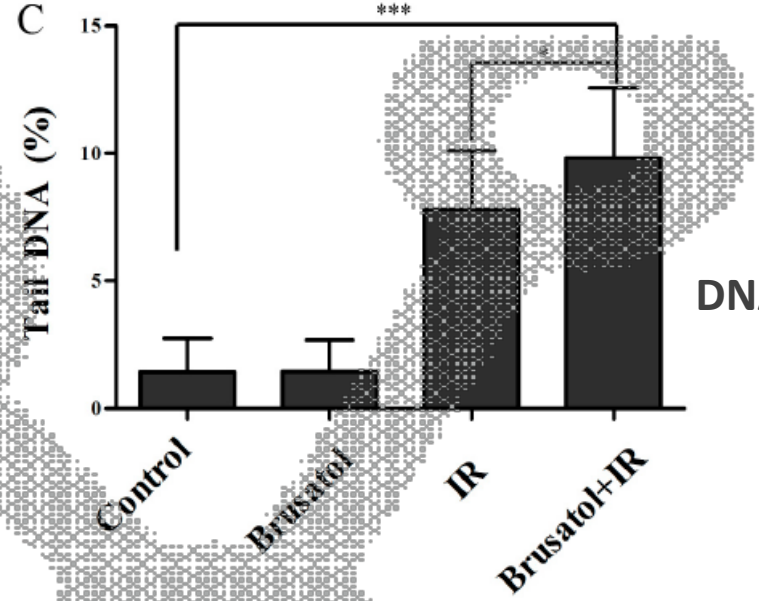
A549 cells were treated with 80 nM for 4 h, and were then subjected to γ irradiation (6 Gy).

Sun X et al. Int J Mol Sci. 2016, 17(7): 997.

ROS



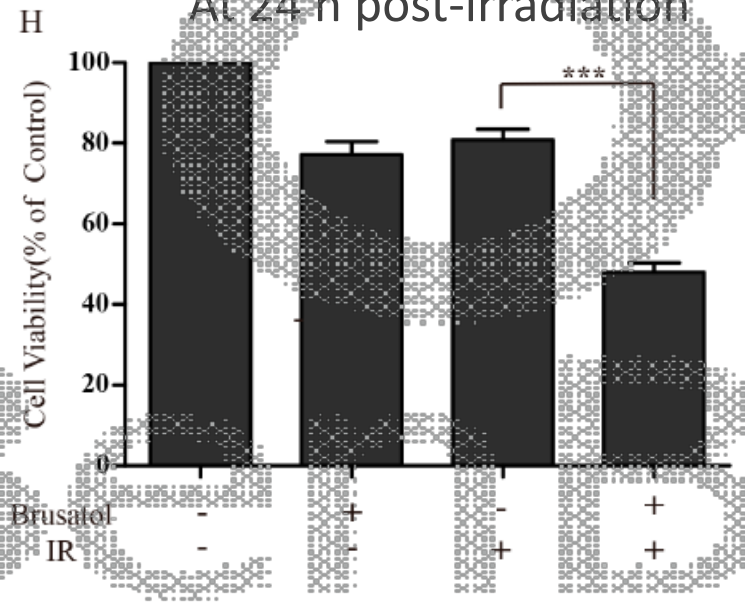
At 4 h post-irradiation



DNA damage

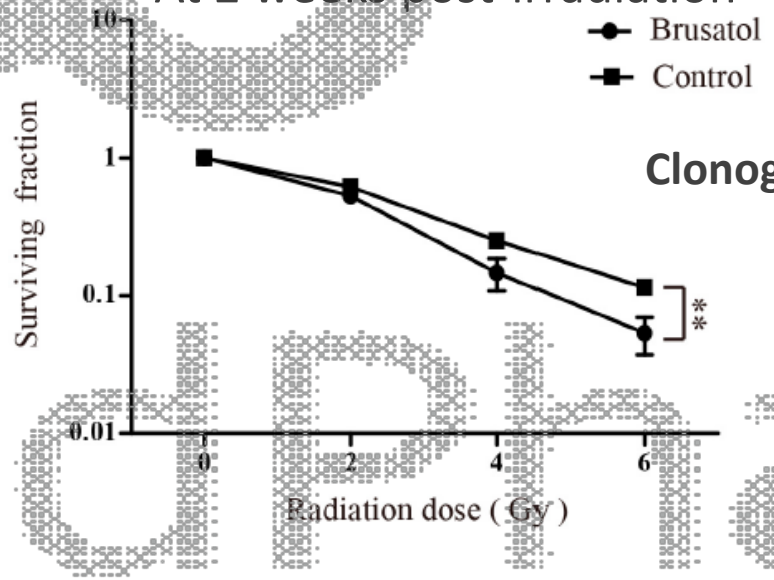
At 24 h post-irradiation

Viability



At 2 weeks post-irradiation

Clonogenic assay



NRF2 inhibitors as radiosensitizing agents

Thank you for attention!

BenBedPhar