

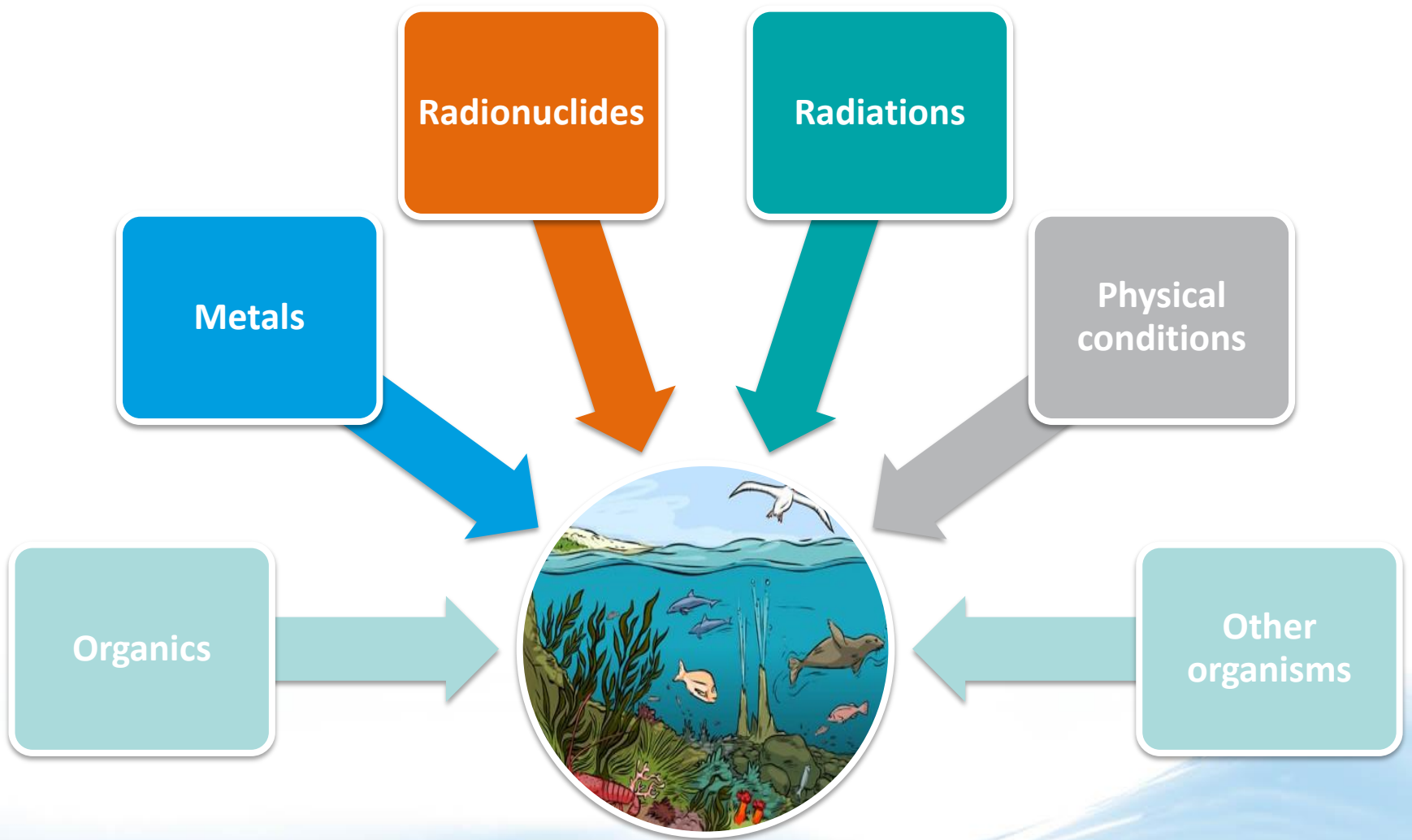
Deciphering multiple stressor effects of gamma radiation and uranium on Atlantic salmon (*Salmo salar*):

Transcriptomics-based mixture modeling

Y. Song, J. Asselman, K.A.C. De Schamphelaere, B. Salbu, and K.E. Tollefsen



Multiple stressors: The reality!



Prediction of combined effect

Concentration addition (CA)

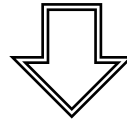
$$\sum_{i=1}^n (c_{Si}/EC_x(Si)) = 1$$



Similar mode of action and target

Survival
Growth
Reproduction

Assumption:
Additive



Independent action (IA)

$$X = 1 - \prod_{i=1}^n (1 - F_i(p_{Si} \cdot (EC_{xmix})))$$



Dissimilar modes of action and targets

Model prediction: Single vs Combined



No deviation



Additivity
(1+1=2)



Deviation

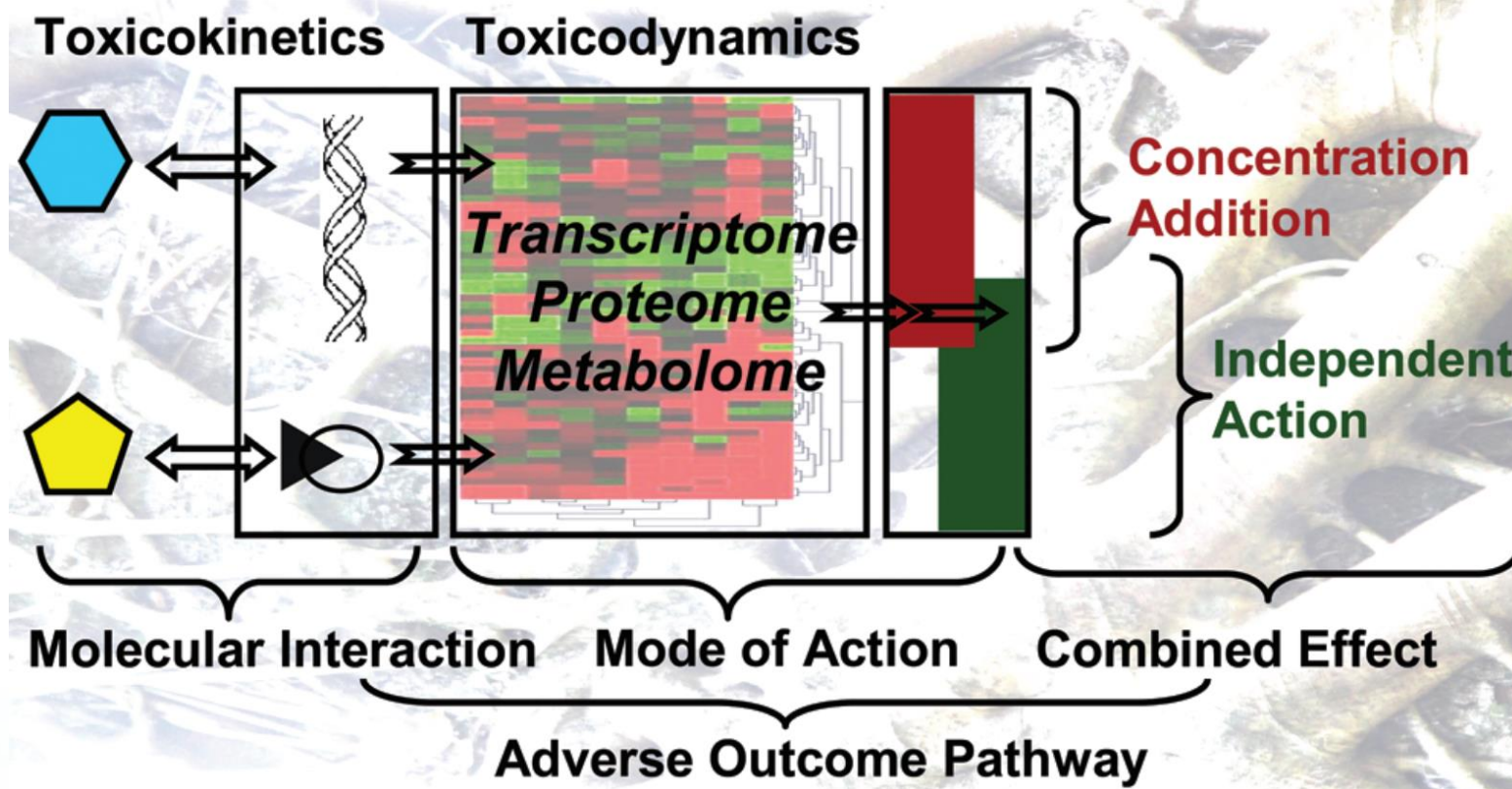


Antagonism
(1+1<2)

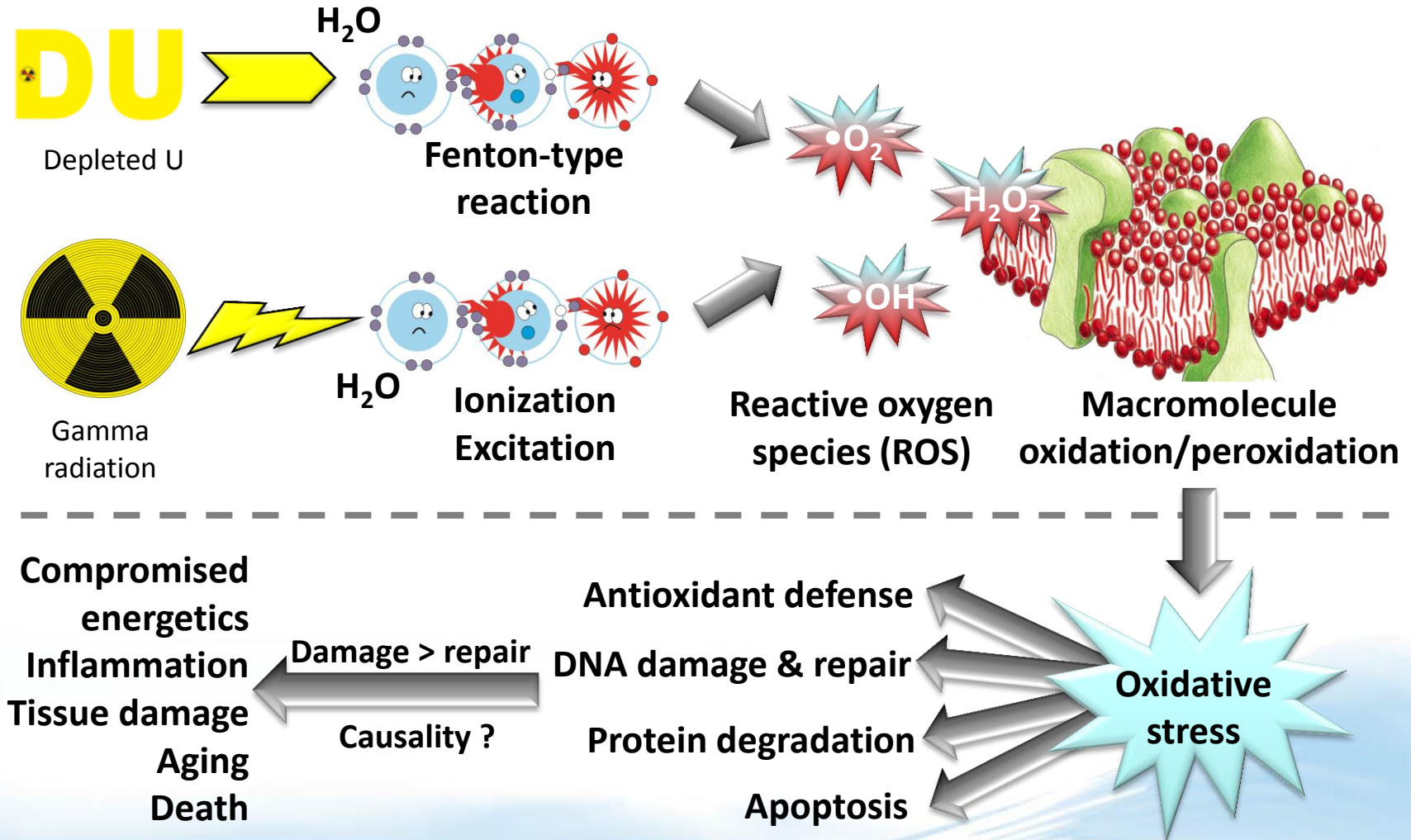


Synergism
(1+1>2)

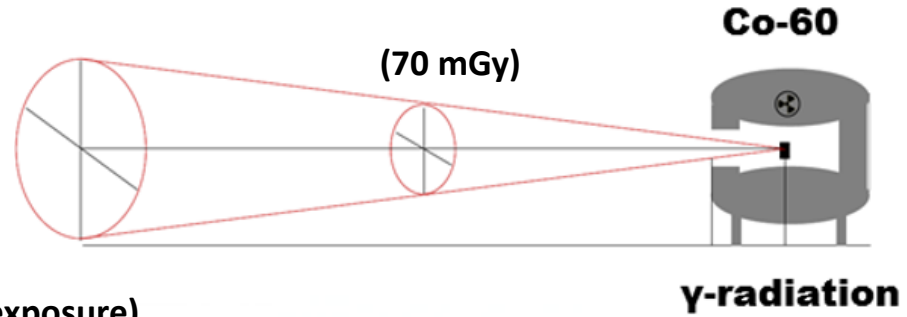
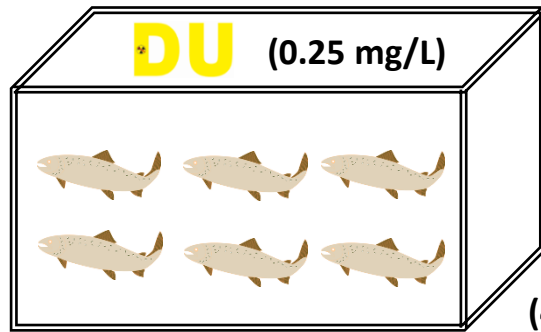
Can we better understand the combined effect based on the OMICS data?



Case study: Combined effect of uranium & gamma radiation on Atlantic salmon



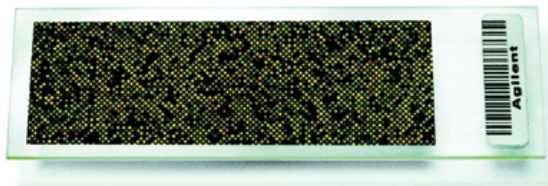
Exposure and hepatic transcriptomic analysis



Liver



RNA



**Transcriptomic analysis
(Microarray)**

Qualitative assessment (mode of action comparison)

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Hepatic transcriptional responses in Atlantic salmon (*Salmo salar*) exposed to gamma radiation and depleted uranium singly and in combination



You Song ^{a,b,*}, Brit Salbu ^a, Hans-Christian Teien ^a, Øystein Evensen ^c, Ole Christian Lind ^a, Bjørn Olav Rosseland ^{a,d}, Knut Erik Tollefsen ^{a,b}

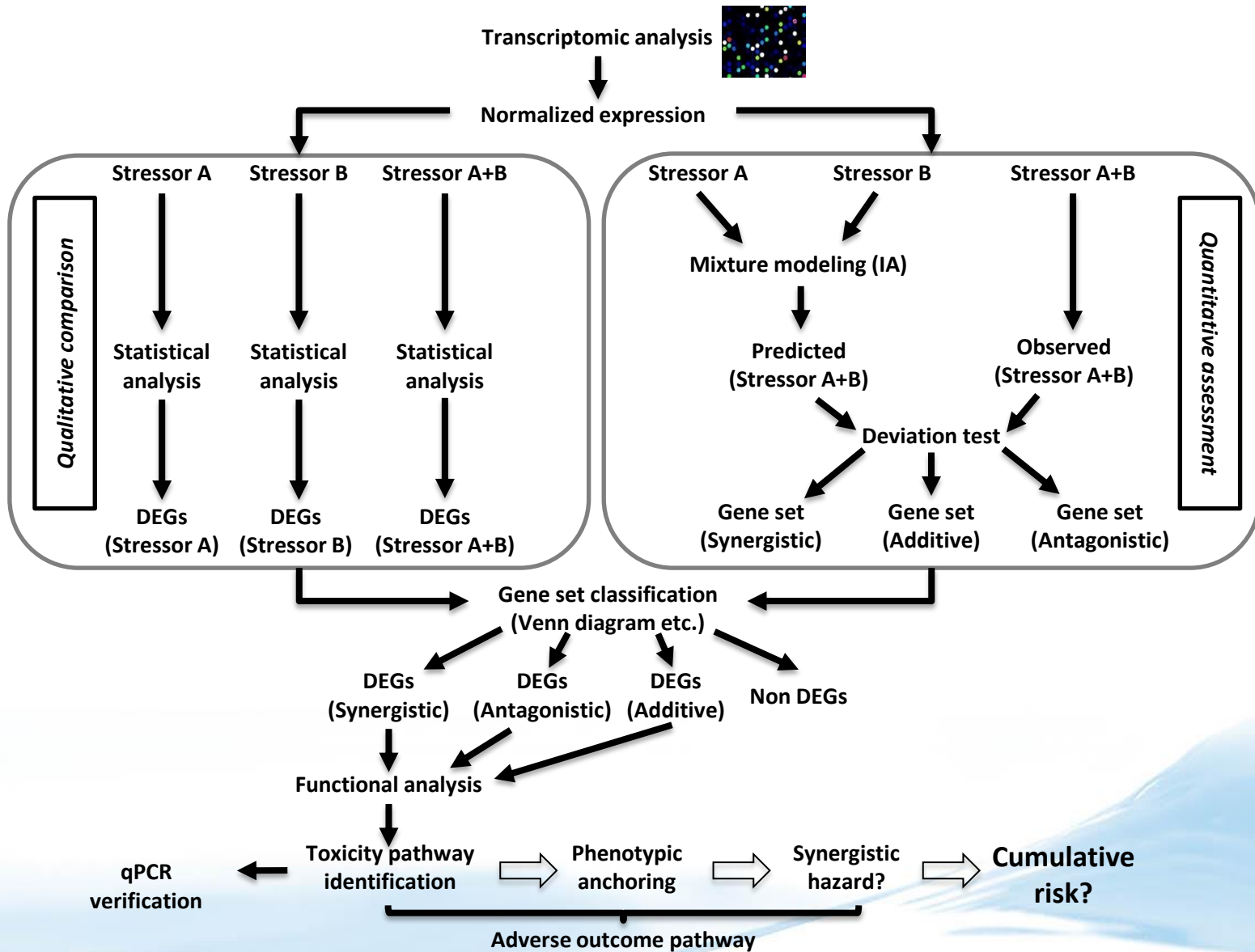
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^b Norwegian Institute for Water Research (NIVA), Gaustadalléen 21, N-0349 Oslo, Norway

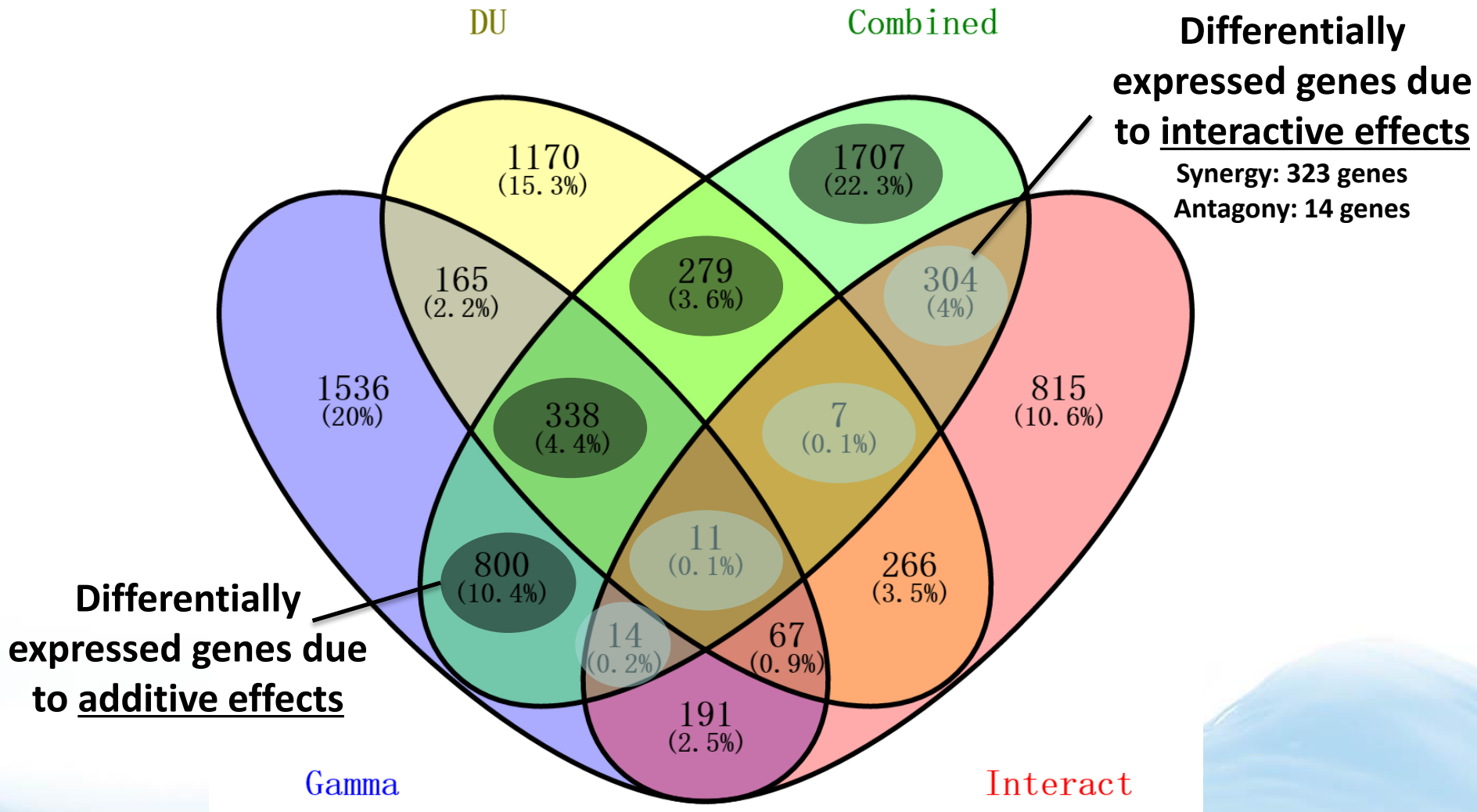
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^d Norwegian University of Life Sciences (NMBU), Department of Ecology and Natural Resource Management (INA), P.O. Box 5003, N-1432 Ås, Norway

Novel data analysis strategies



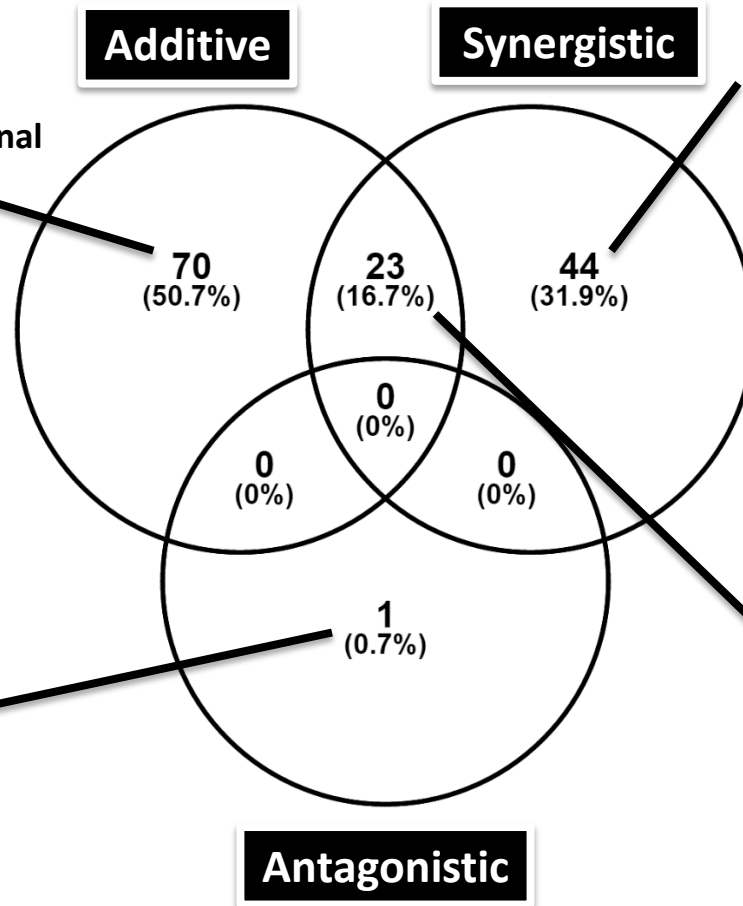
Combined effect on gene expression



Functional analysis of genes (pathways)

- Antigen Presentation Pathway
- Apoptosis Signaling
- Calcium-induced T Lymphocyte Apoptosis
- DNA Methylation and Transcriptional Repression Signaling
- Mitochondrial Dysfunction
- NRF2-mediated Oxidative Stress Response
- Oxidative Phosphorylation
- PPAR α /RXR α Activation
- Protein Ubiquitination Pathway
- Superoxide Radicals Degradation
- Xenobiotic Metabolism Signaling

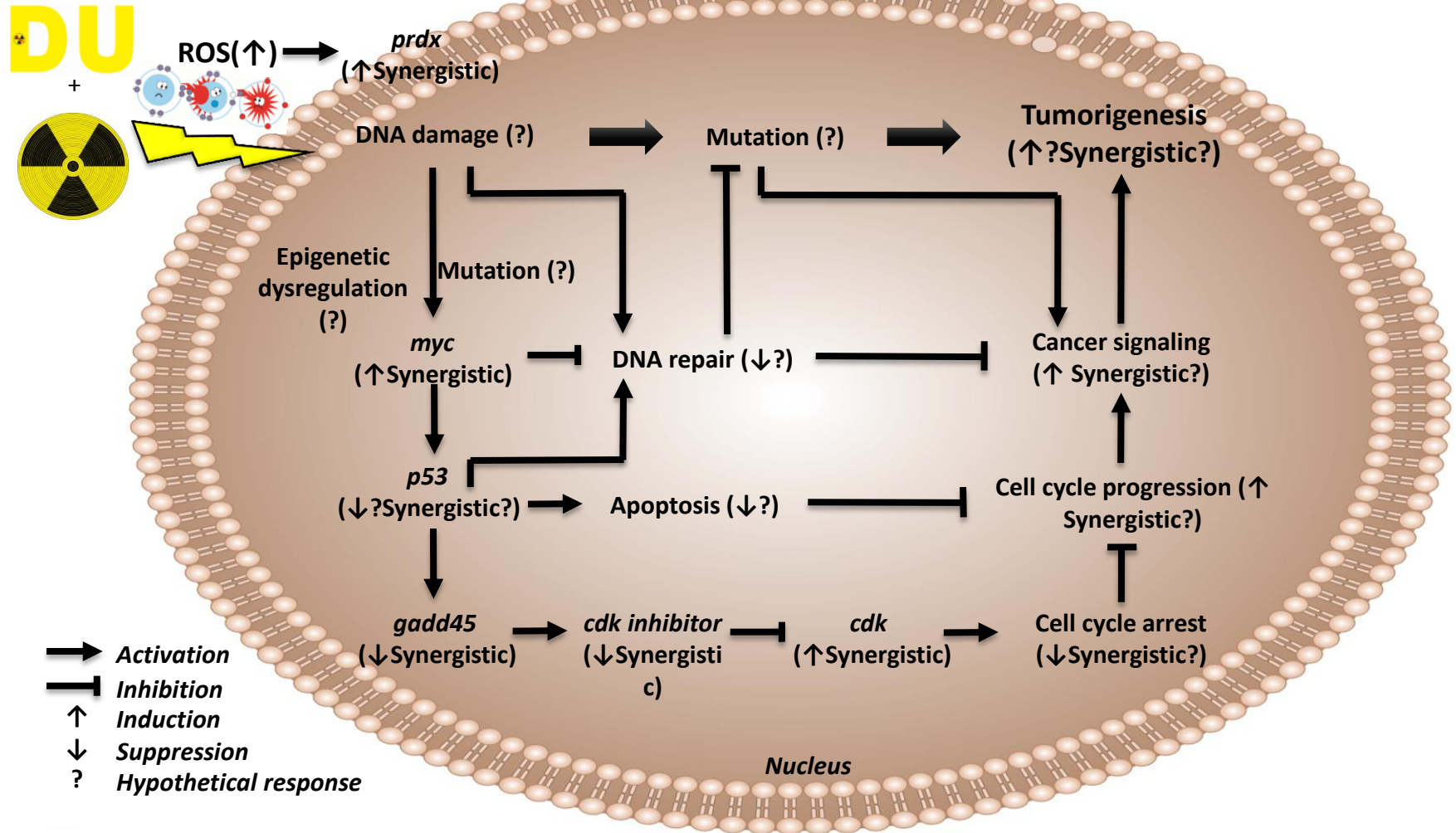
•Role of BRCA1 in DNA Damage Response



- Fatty Acid β -oxidation III
- p53 Signaling
- GADD45 Signaling
- SAPK/JNK Signaling
- Sumoylation Pathway
- ATM Signaling

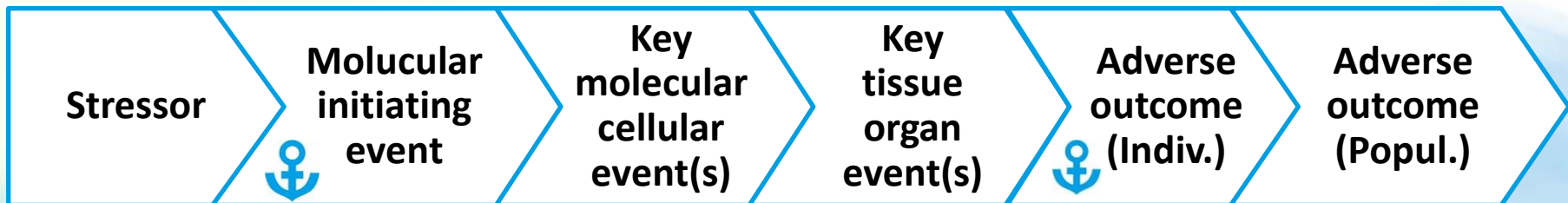
- B Cell Receptor Signaling
- Molecular Mechanisms of Cancer
- IL-8 Signaling

Identification of synergistic toxicity pathway



Summary

- Potential interactive effects of gamma and uranium identified at the molecular level
- A toxicity pathway leading to tumorigenesis potentially synergized due to interactive effect
- A conceptual quantitative approach proposed for better understanding of synergy using OMICS
- Future: AOP-assisted cumulative hazard assessment



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Thank you!