



**FRIDA:**

*FLASH Radiotherapy with high  
Dose-rate particle beams*

**WP1 - The UHDR *in vitro* database**

Mach 4, 2026

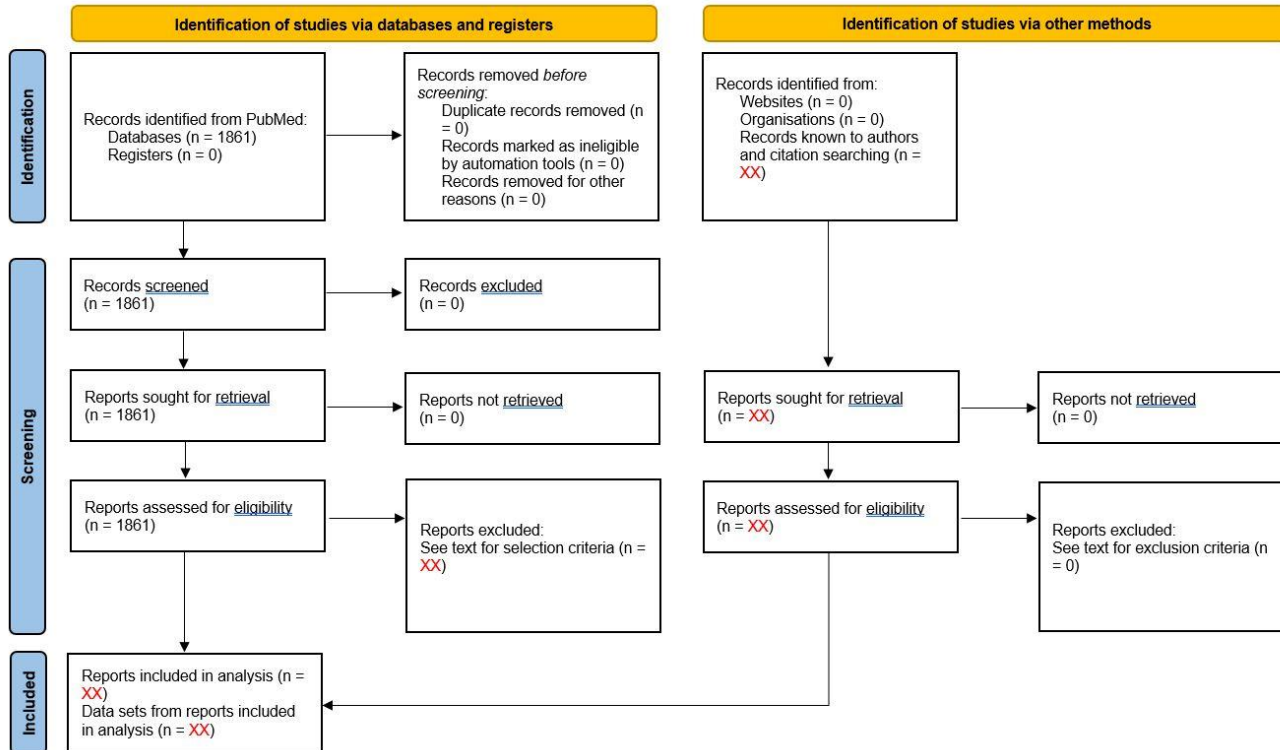
A Attili, T Böhlen, E Scifoni, F Tommasino, F Zerakni, R Moeckli.

# Systematic collection and analysis for insights in the FLASH mechanism

Collection of CDR and UHDR *in vitro* cell survival data for given **dose**, **pO<sub>2</sub>**, **radiation source** and **temporal dose delivery structure**.

1. Systematic review and meta analysis of CDR and UHDR in vitro data: compare historical data and mechanistic explanation with more recent data focussing on FLASH (year range: 1967 - 2024)
2. To what extent (based on the historical data) can the observed differences between CDR and UHDR in vitro data be explained by the radiolytic oxygen depletion (ROD) can contribute to a given extent, and to what extent is there a sign of other mechanisms (e.g. FLASH)?
3. Information from in vitro are transferable to in vivo? Comparison with behaviour of FLASH effect of in vivo data.
4. Easy access to historical in vivo data for the scientific community.

# Record and report identification



Publications with mammalian cell survival data from UHDR irradiation ( $\geq 30$  Gy/s)

PubMed query:  
“FLASH” AND  
 (“RADIOTHERAPY” OR  
 “RADIATION” OR  
 “IRRADIATION”)

Old UHDR publications added manually from various sources.

30 Publications, ~2500 data points

# Database structure

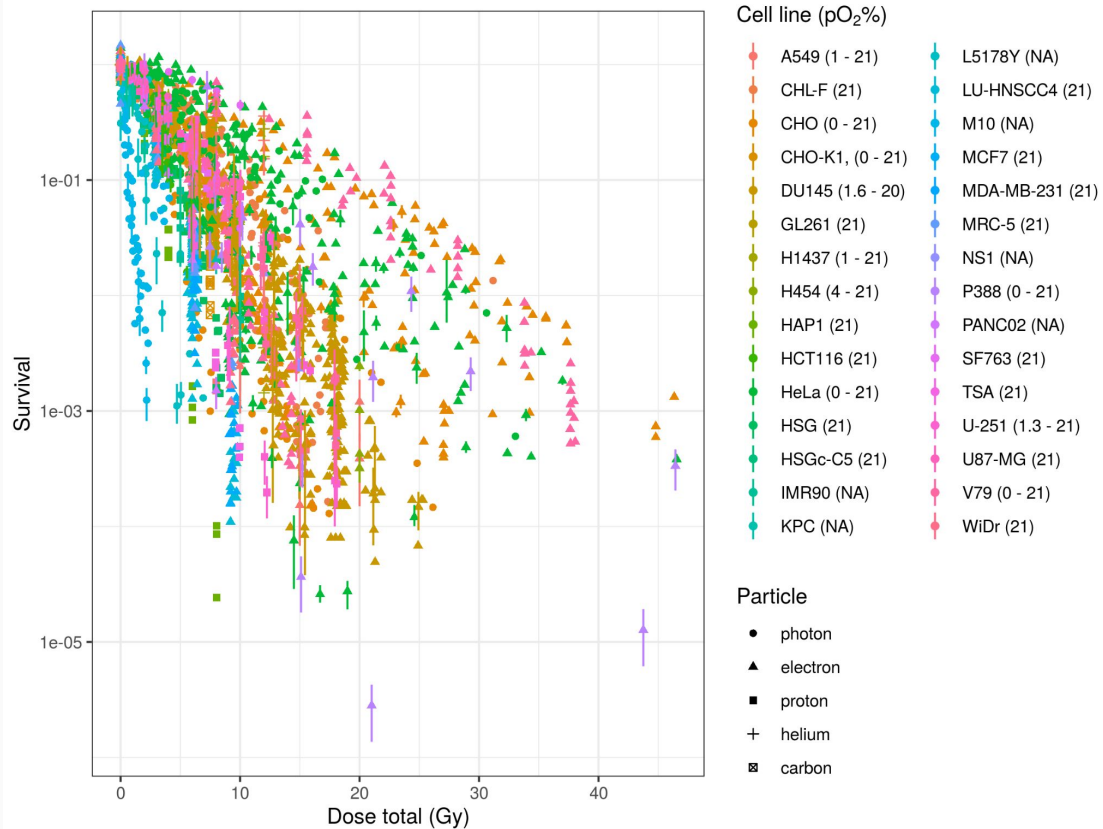
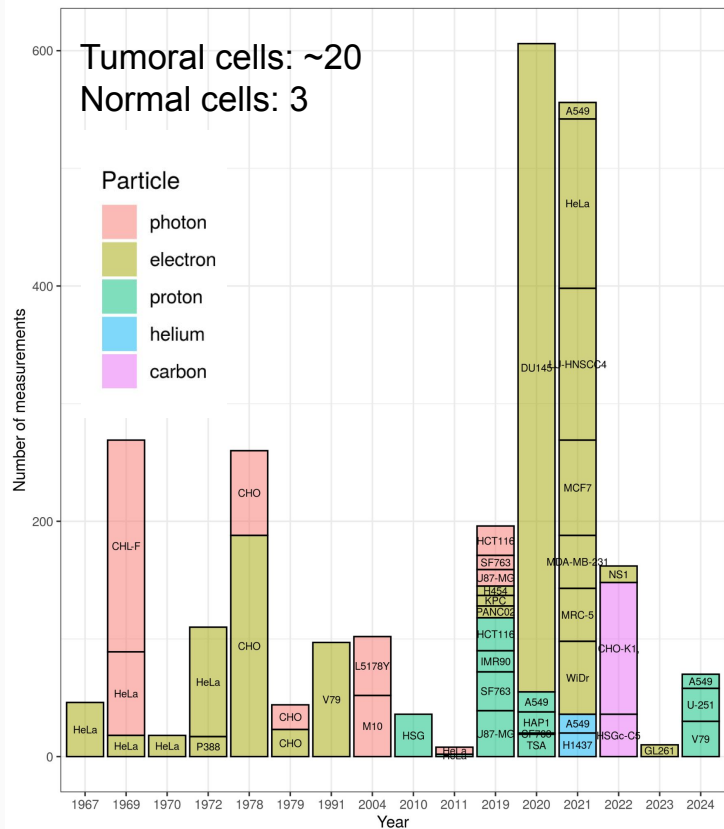


IDs
Reference, Set ID, Data ID, Data Source, Label
Bio
In vivo / in vitro, Biological system, Environment, pO2 (%), Endpoint, Value, Value min, Value max, Min/max uncertainty type
Radiation
Source, Scanning type, Particle, Energy (MeV/u), LET (keV/μm), LET type
Dose time structure
Dose total (Gy), Dose per pulse (Gy), Dose rate avg. (Gy s <sup>-1</sup> ) Dose rate inst. (Gy s <sup>-1</sup> ), Number of pulses, Exposure time (s), Pulse duration (ns), PRF (Hz)

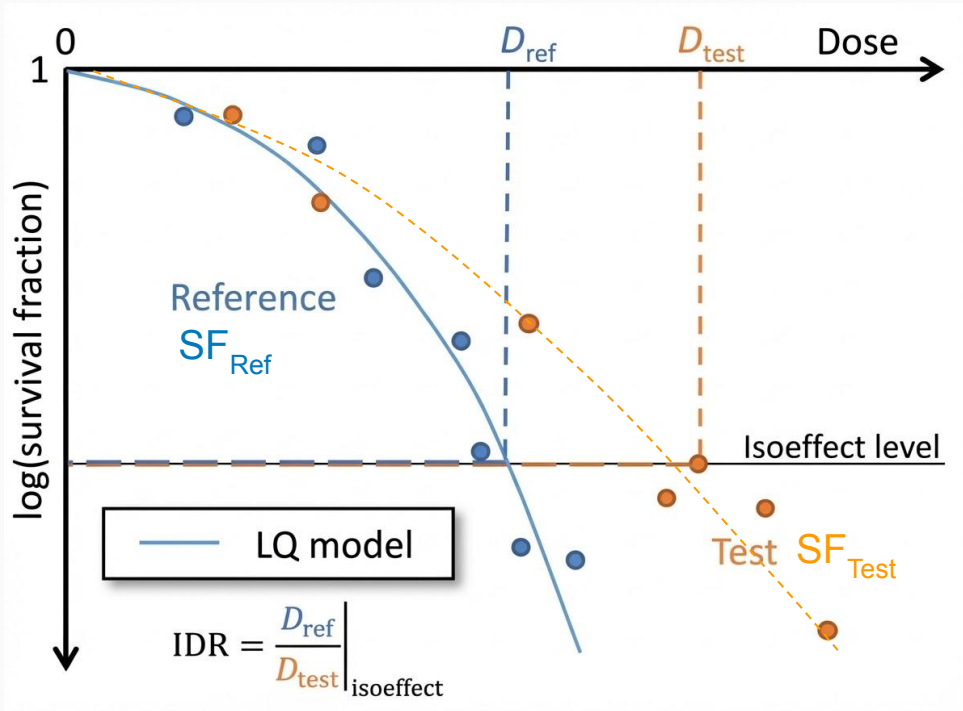
variable	pre (%)	post (%)
Energy (MeV/u)	92.70	94.79
LET (keV/μm)	11.35	17.72

variable	pre (%)	post (%)
Dose per pulse (Gy)	39.85	63.78
Dose rate avg. (Gy s <sup>-1</sup> )	82.97	85.56
Dose rate inst. (Gy s <sup>-1</sup> )	46.80	58.26
Exposure time (s)	52.01	85.56
Number of pulses	61.27	63.78
PRF (Hz)	26.25	26.25
Pulse duration (ns)	48.80	48.80

# Overview of the data



# Evaluation of isoeffective dose ratios (IDR)

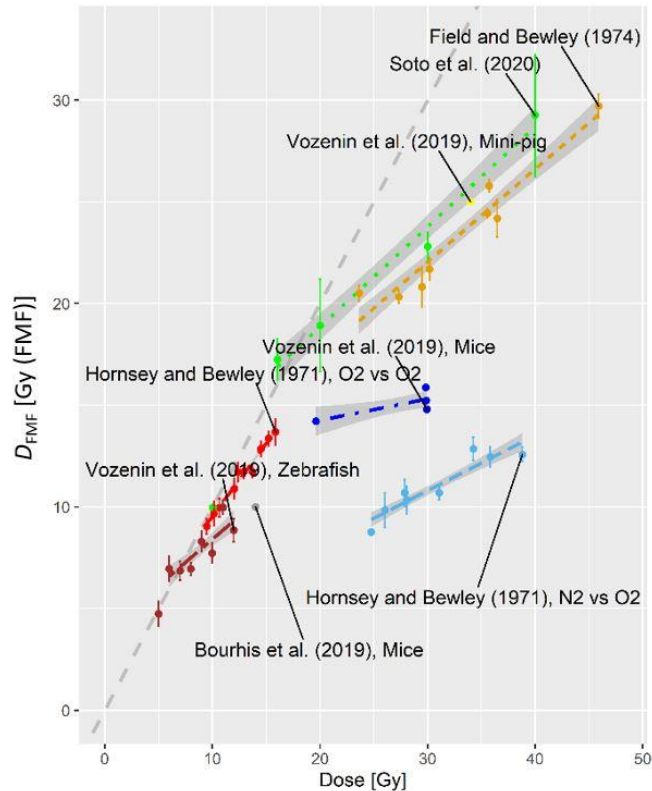


$$IDR_T = \frac{D_{Tref}}{D_{Ttest}} \Big|_{\text{isoeffect}}$$

$$SF_{ref}(D) = e^{-\alpha D - \beta D^2}$$

$$SF_{test}(D) = e^{-\alpha IDR(D) \cdot D - \beta (IDR(D) \cdot D)^2}$$

# IDR(D) : “piecewise” fit and ROD hypothesis



IDR-weighted dose (Gy(IDR))

$$D_{IDR} = D \times IDR(D)$$

“Piecewise” phenomenological function

$$IDR(D) = \begin{cases} 1 & \text{for } D \leq D_T \\ IDR_{asy} + (1 - IDR_{asy}) \frac{D_T}{D} & \text{for } D > D_T \end{cases}$$

Radiolytic oxygen depletion (ROD) [Boscolo et al. 2021]

$$IDR_T(pO_2) = \frac{D_{Tref}}{D_{Ttest}} \Big|_{\text{isoeffect}} = \frac{OER_{dyn}(pO_2)}{OER(pO_2)} \Big|_{\text{isoeffect}}$$

# Identification of the “reference” and “test” sets

$IDR_T$  Reference sets:

CDR (ADR < 2 Gy/s)

- 1)  $pO_2 > 19\%$
- 2)  $pO_2 \leq 19\%$

$IDR_T$  Test sets:

UHDR (ADR > 90 Gy/s)

(same  $pO_2$  as Ref.)

$IDR_{O_2}$  Reference set:

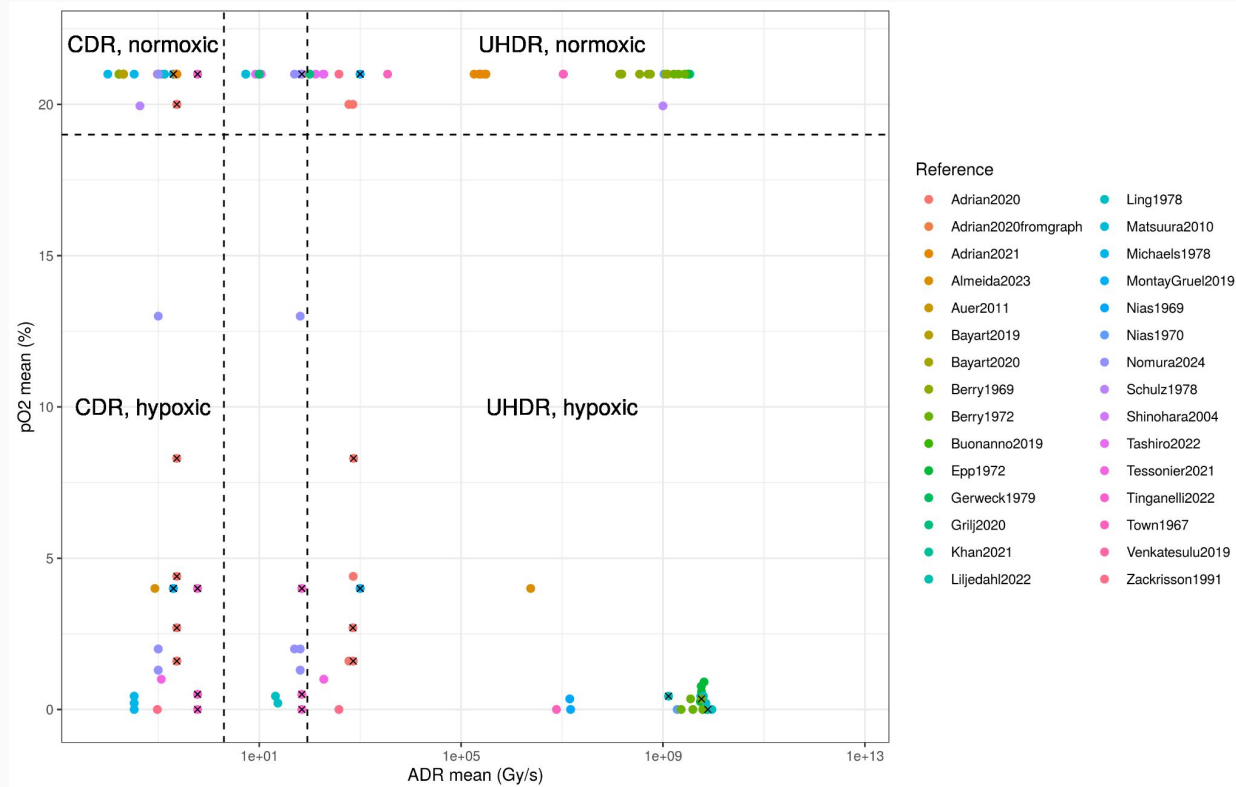
UHDR (ADR > 90 Gy/s)

$pO_2 > 19\%$

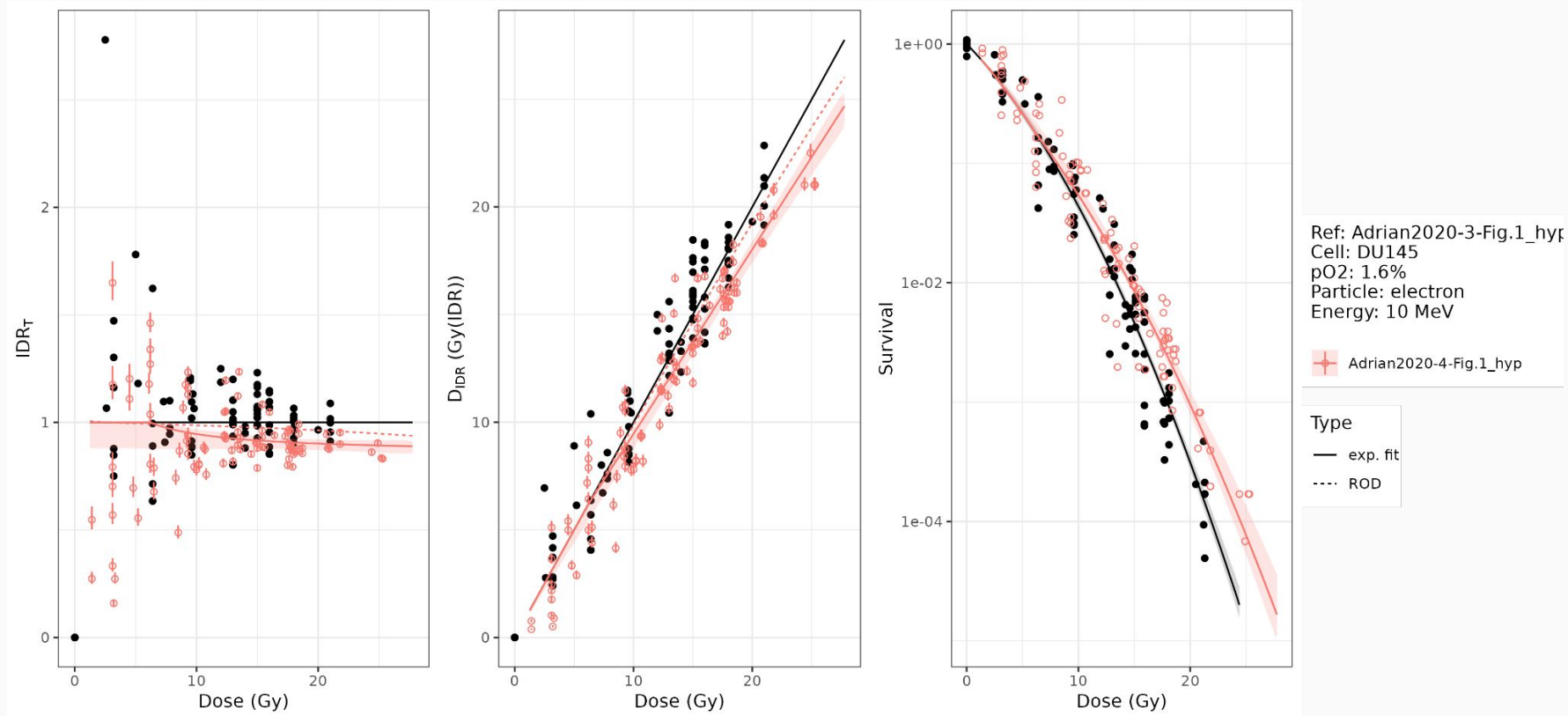
$IDR_{O_2}$  Test set:

UHDR (ADR > 90 Gy/s)

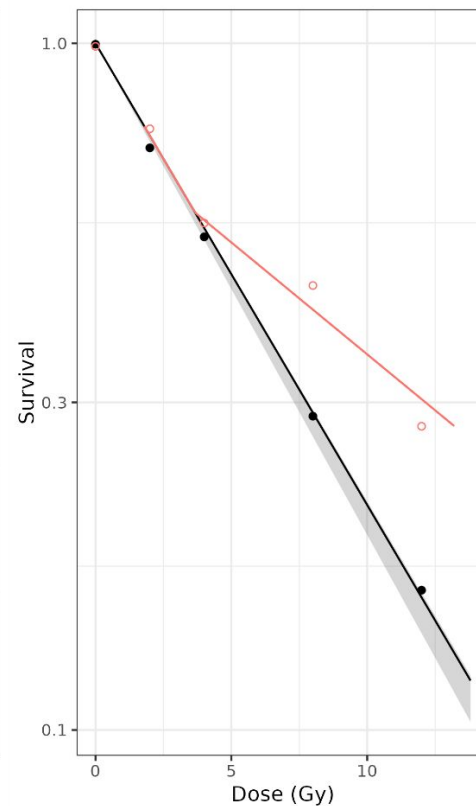
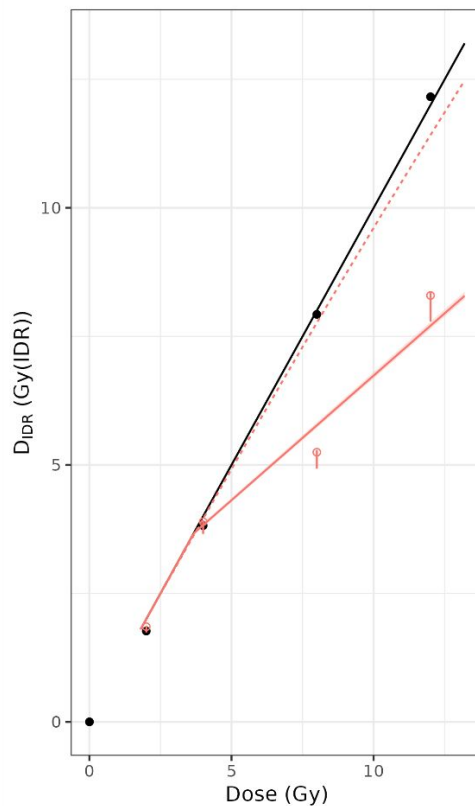
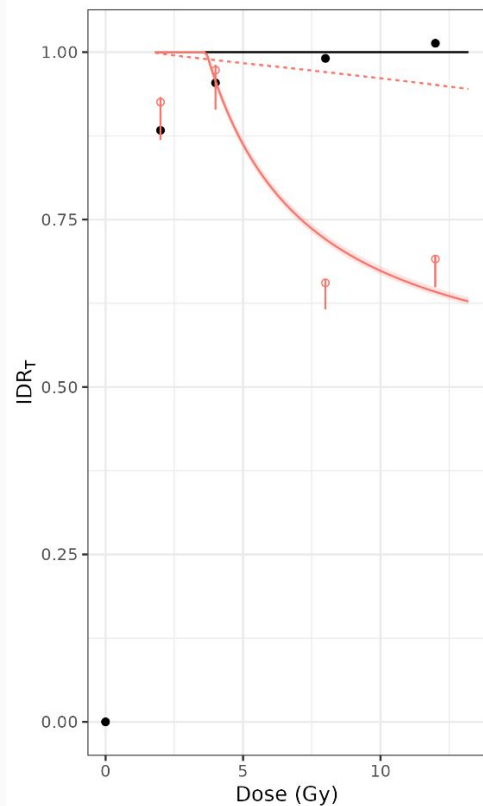
$pO_2 \leq 19\%$



# Example of analysis (Adrian et al. 2020)



# Example of analysis (Tessonier et al. 2021)



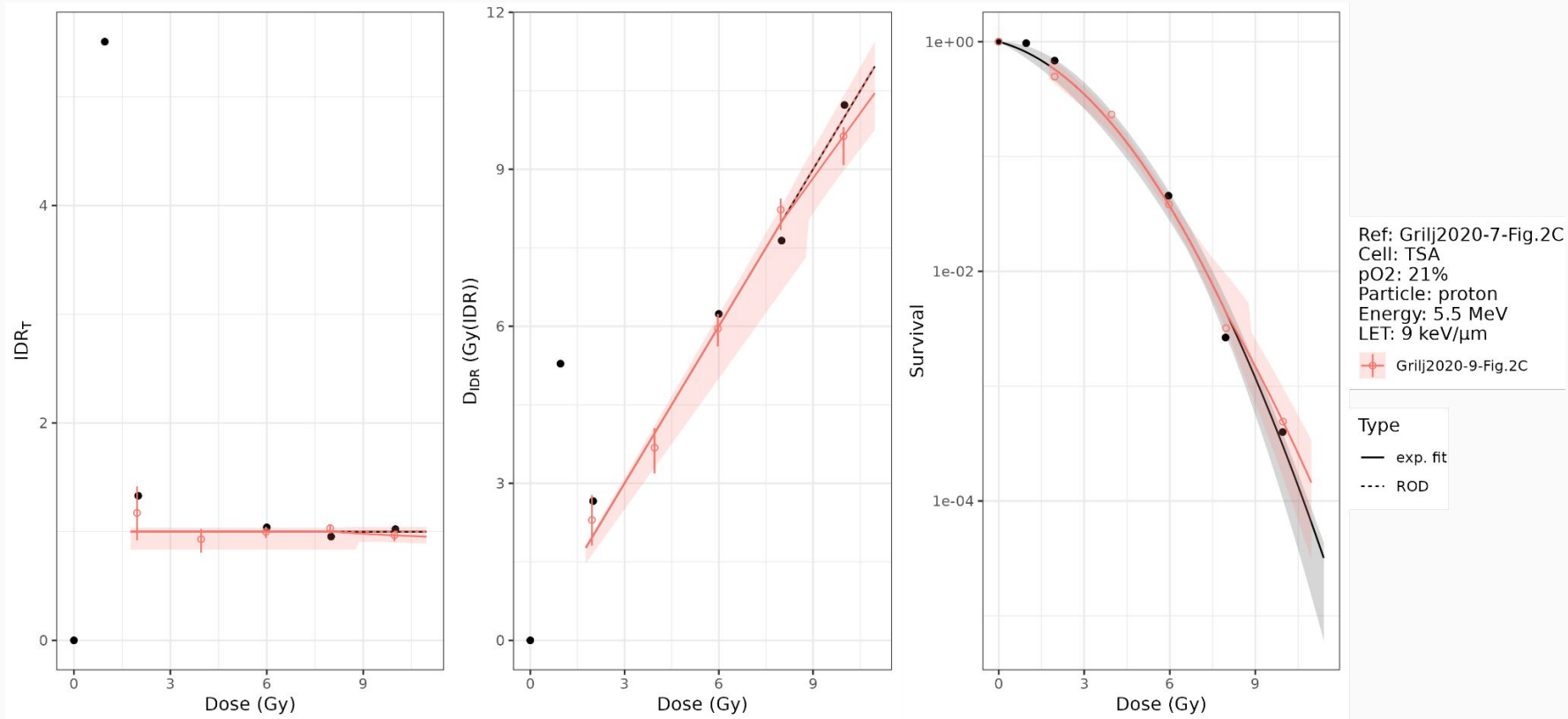
Ref: Tessonier2021-3-Fig.5B  
Cell: H1437  
pO<sub>2</sub>: 1%  
Particle: helium  
Energy: 12.08 MeV/u  
LET: 16 keV/μm

Tessonier2021-4-Fig.5B

Type

— exp. fit  
- - - ROD

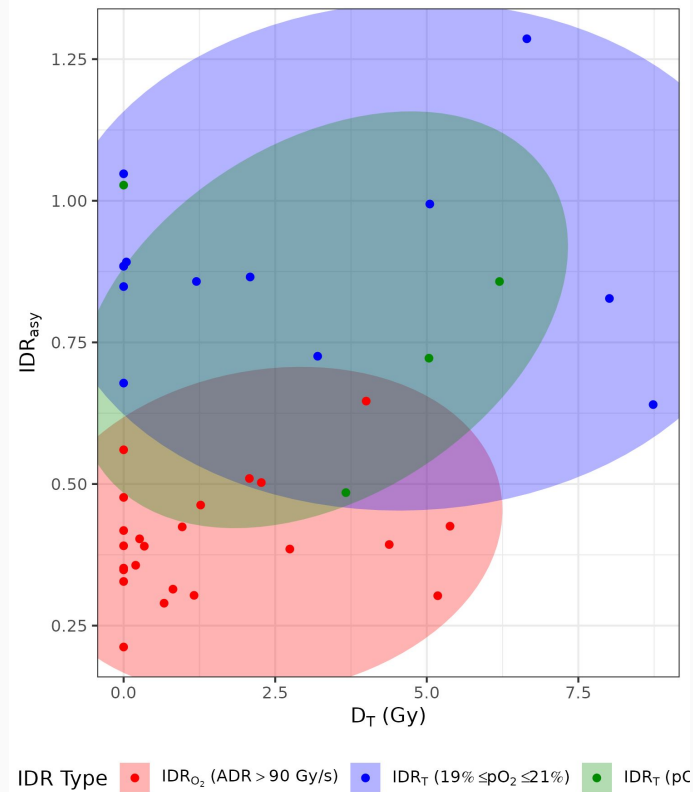
# Example of analysis (Grilj et al. 2020)



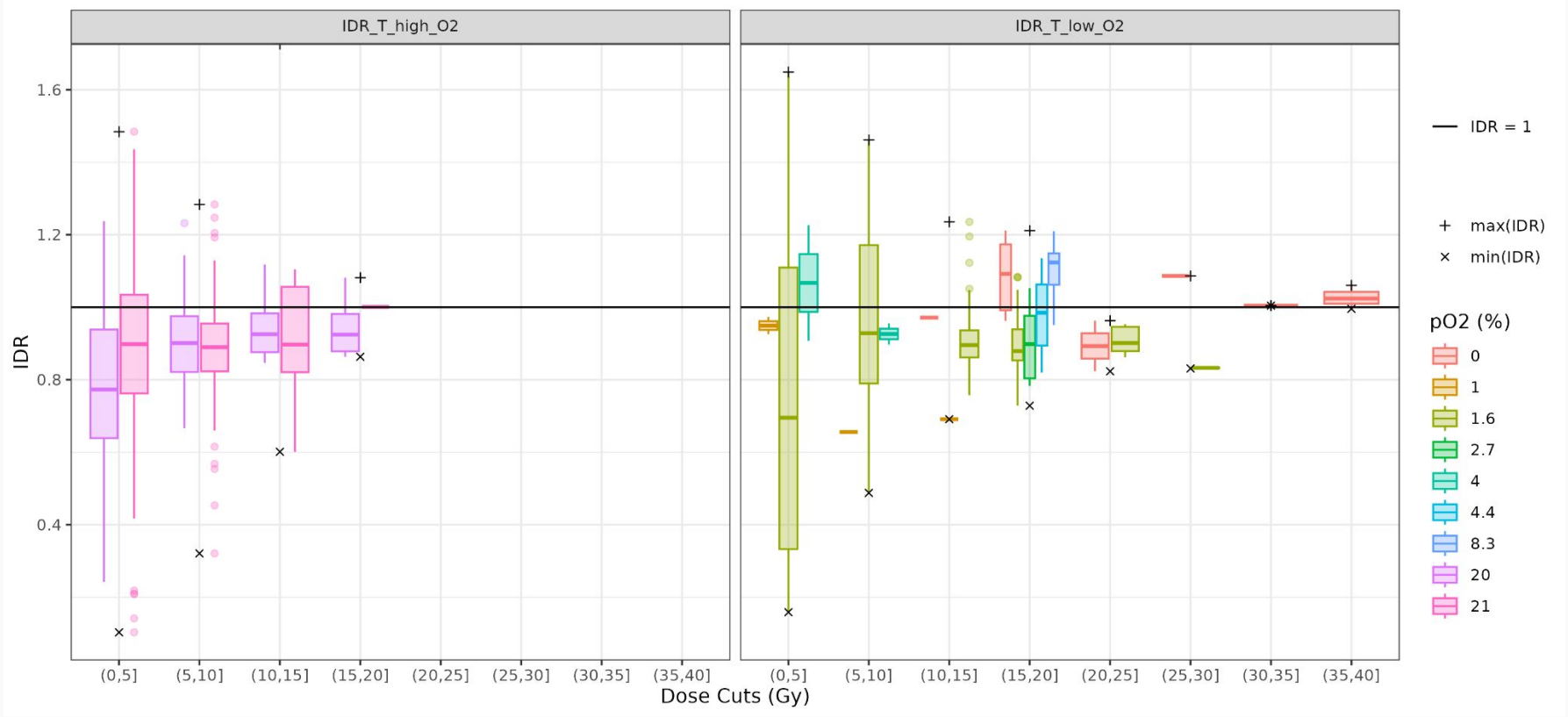
# Correlations

Table 1: Correlation coefficients grouped by variable

	pearson	kendall	spearman	IDR_type	variable
1	-0.34	-0.20	-0.28	All data	test_Dose
2	0.15	0.09	0.12	IDR_T_high_O2	
3	-0.25	-0.16	-0.22	IDR_O2_high_ADR	
4	0.18	0.11	0.16	IDR_T_low_O2	
5	0.47	0.49	0.62	All data	test_pO2
6	0.00	-0.01	-0.01	IDR_T_high_O2	
7	0.59	0.65	0.80	IDR_O2_high_ADR	
8	0.21	0.10	0.12	IDR_T_low_O2	
9	-0.52	-0.36	-0.50	All data	test_ADR
10	-0.09	-0.15	-0.20	IDR_T_high_O2	
11	-0.45	-0.39	-0.55	IDR_O2_high_ADR	
12	0.09	0.03	0.04	IDR_T_low_O2	
13	-0.58	-0.37	-0.52	All data	test_DPP
14	-0.23	-0.16	-0.23	IDR_T_high_O2	
15	-0.50	-0.39	-0.55	IDR_O2_high_ADR	
16	-0.10	0.03	0.04	IDR_T_low_O2	



# IDR vs. Dose vs. pO2 : global trends



# In vitro → in vivo? (still in discussion)

Effect	Observation (in vitro)	Feature comparison (in vitro vs. preclinical data)
Dose dependence	For some datasets, IDR decrease with increasing dose.	Consistent only for a subset of data. Global trend not clear.
Dose dependence: piecewise linear behaviour	For some datasets, IDRT as a function of dose exhibits an approximately piecewise linear behaviour	Consistent only in selected dataset.
Temporal delivery structure dependencies	Differential survival effects between UHDR and CDR. Prolonged irradiations, tend to diminish differential sparing.	Consistent, but lack of dedicated in vitro dose rate scan data.
Fractionation	Reduction of FLASH sparing with decreasing dose per fraction.	Likely consistent, but in vitro fractionation data are lacking.
Tissue-related	Differential sparing effects are observed in normal-tissue-derived cell lines and in tumoral cell, depending on dose and pO <sub>2</sub>	Inconsistent. Majority of experiment with tumoral cells.
pO <sub>2</sub>	Oxygen tension modulates the magnitude of the differential sparing effect. Normoxic cells show in general less sparing	Consistent