Advancing Gamma-tocotrienol as a Prophylactic Radiation Countermeasure: Nonhuman Primate Efficacy and Multi-omics Biomarkers

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The views expressed do not necessarily represent the opinions or policies of the Armed Forces Radiobiology Research Institute, the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States.

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This research protocol was approved by the USUHS IACUC in accordance with all applicable Federal regulations.

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Promising Radioprotectors under Advanced Development

- **Though we study a large number of MCM candidates being investigated at AFRRI, specifically in NHP models, two prophylactic agents have been identified and patented by AFRRI**

  - **Gamma-tocotrienol – Vitamin E component**
  - **Genistein - Soy isoflavone – Nanosuspension/BIO 300**

- **Both are under advanced development and being studied in NHP models**

AFRRI as a Unique Institution for Radiation MCM Development:

- All radiation sources under one roof
- State of the art dosimetry
- Vivarium with rodents to NHP

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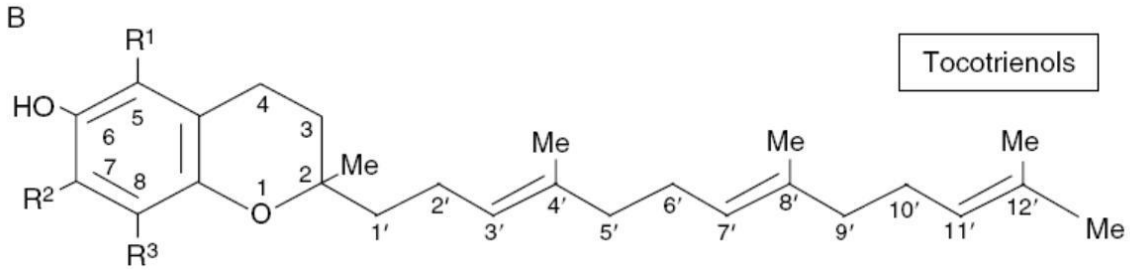
Gamma-tocotrienol (GT3)



- **Naturally occurring isoform of vitamin E**
- **Tocotrienols studied in several clinical trials studies for unrelated indications (gamma-, delta-tocotrienol and tocotrienol rich fraction)**
- **Cholesterol lowering properties: Inhibition of Hydroxymethylglutaryl Coenzyme A reductase (HMGCR)**
- **Reduces type II diabetes**
- **Anti-inflammatory and potent antioxidant**

- **Route of administration: Subcutaneous/intramuscular**
- **Mechanism of action: Antioxidant/Free radical scavenger**

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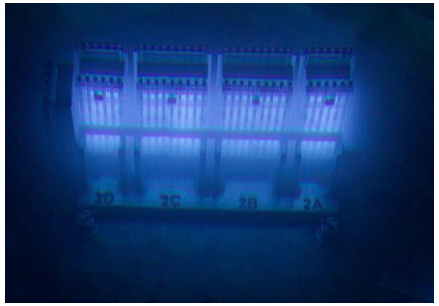
Overview of GT3 work



Panoramic field TBI

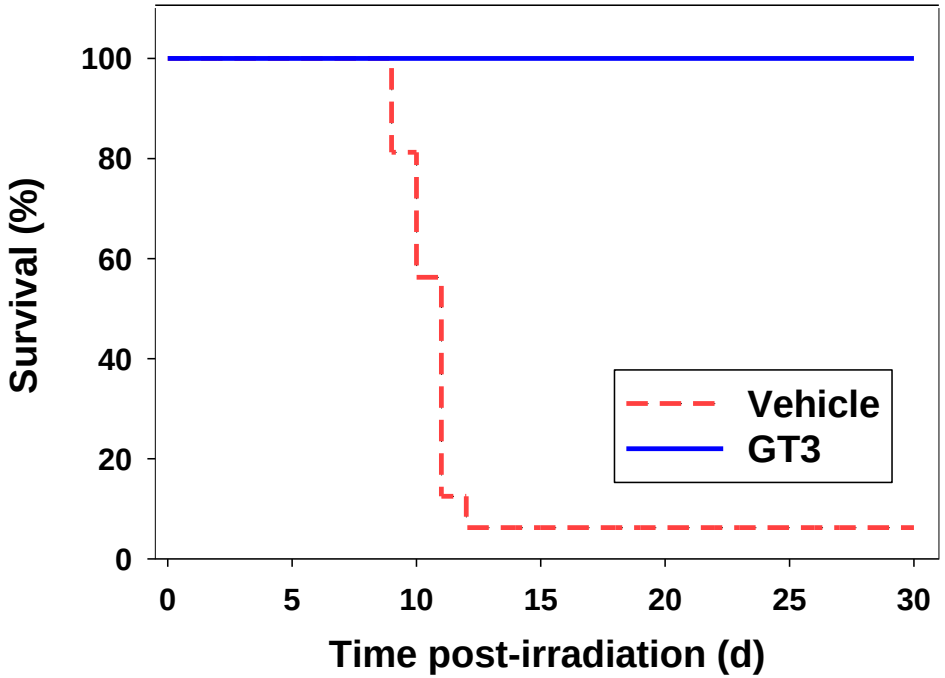
Collimated beam PBI

Various doses

- Survival
- Mechanistic Investigation: Hematopoietic and GI injury using TBI and PBI models of NHP
- G-CSF induction, abrogation of protection, mobilization of progenitors
- **Biomarkers:**
  - Cytokines
  - Metabolomics/Lipidomics
  - Proteomics
  - Transcriptomics
  - miRNA

Murine Model: Radioprotective efficacy of GT3 in murine model against TBI

9.2 Gy ($LD_{70/30}$) TBI



Protects mice against as high as 11.5 Gy TBI gamma-irradiation, DRF 1.3

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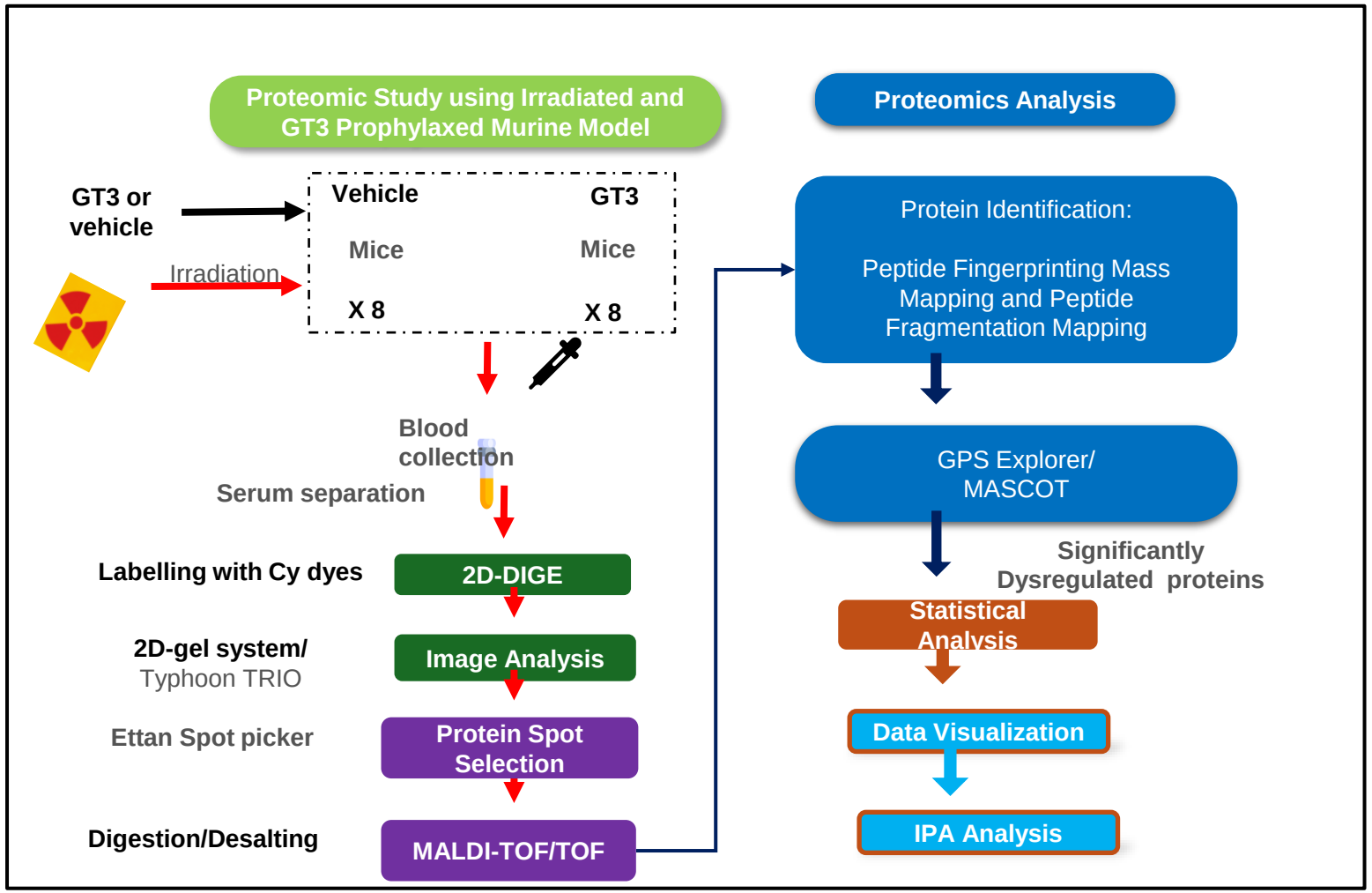
Proteomics: Schematic of study sample preparation and data analysis



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Serum proteins reflecting a change in expression in response to TBI and reversal with prophylactic treatment of GT3

Spot	UniProt Name	Protein	TBI : No TBI	p-value	TBI : GT3	p-value	GT3 : No TBI	p-value
61	A1AG1_MOUSE	Alpha-1-acid glycoprotein 1	8.8	2.60E-12	-5.9	3.10E-11	51.7	1.30E-15
80	A1AT1_MOUSE	Alpha-1-antitrypsin 1-1	2.0	4.50E-06	-2.3	2.80E-10	4.7	4.60E-09
67	A2M_MOUSE	Alpha-2-macroglobulin	1.5	1.20E-05	-3.0	3.60E-11	4.5	9.20E-11
54	ALBU_MOUSE	Serum albumin	2.7	4.00E-04	-3.9	7.50E-09	10.4	3.20E-07
29	APOH_MOUSE	Beta-2-glycoprotein 1	-2.1	1.60E-12	2.6	3.20E-10	-5.4	2.00E-12
15	CFAB_MOUSE	Complement factor B	1.8	3.50E-08	-2.3	6.40E-10	4.1	1.60E-11
81	CLUS_MOUSE	Clusterin	1.7	1.20E-10	-1.9	8.00E-10	3.4	5.70E-12
47	CO3_MOUSE	Complement C3	2.0	5.60E-04	-1.6	5.60E-04	3.3	4.40E-05
14	EGFR_MOUSE	Epidermal grow th factor receptor	2.0	2.70E-08	-1.6	8.70E-08	3.3	2.80E-11
55	Q91XL1_MOUSE	Leucine-rich alpha-2-glycoprotein precursor	4.1	1.10E-06	-3.5	1.30E-09	14.2	3.30E-09
24	HEMO_MOUSE	Hemopexin	1.9	2.40E-06	-7.7	1.50E-11	14.4	6.30E-13
123	HPT_MOUSE	Haptoglobin	3.5	1.60E-10	-2.7	2.80E-10	9.4	1.70E-12
72	ITIH4_MOUSE	Inter alpha-trypsin inhibitor, heavy chain 4	1.8	1.10E-04	-2.0	5.00E-08	3.6	2.00E-08
109	K2C73_MOUSE	Keratin, type II cytoskeletal 73	4.3	2.80E-06	-2.3	5.00E-06	9.8	4.00E-08
25	KNG1_MOUSE	Kininogen-1	1.6	2.10E-03	-3.0	8.00E-10	4.7	9.30E-08
97	MBL2_MOUSE	Mannose-binding protein C	1.8	5.80E-06	-1.8	8.00E-09	3.1	1.20E-08
112	MUP6_MOUSE	Major urinary protein 6	1.7	4.20E-06	-2.3	7.80E-09	3.9	2.10E-11
130	SAA2_MOUSE	Serum amyloid A-2 protein	19.5	3.40E-14	-1.9	4.10E-07	36.8	1.50E-14

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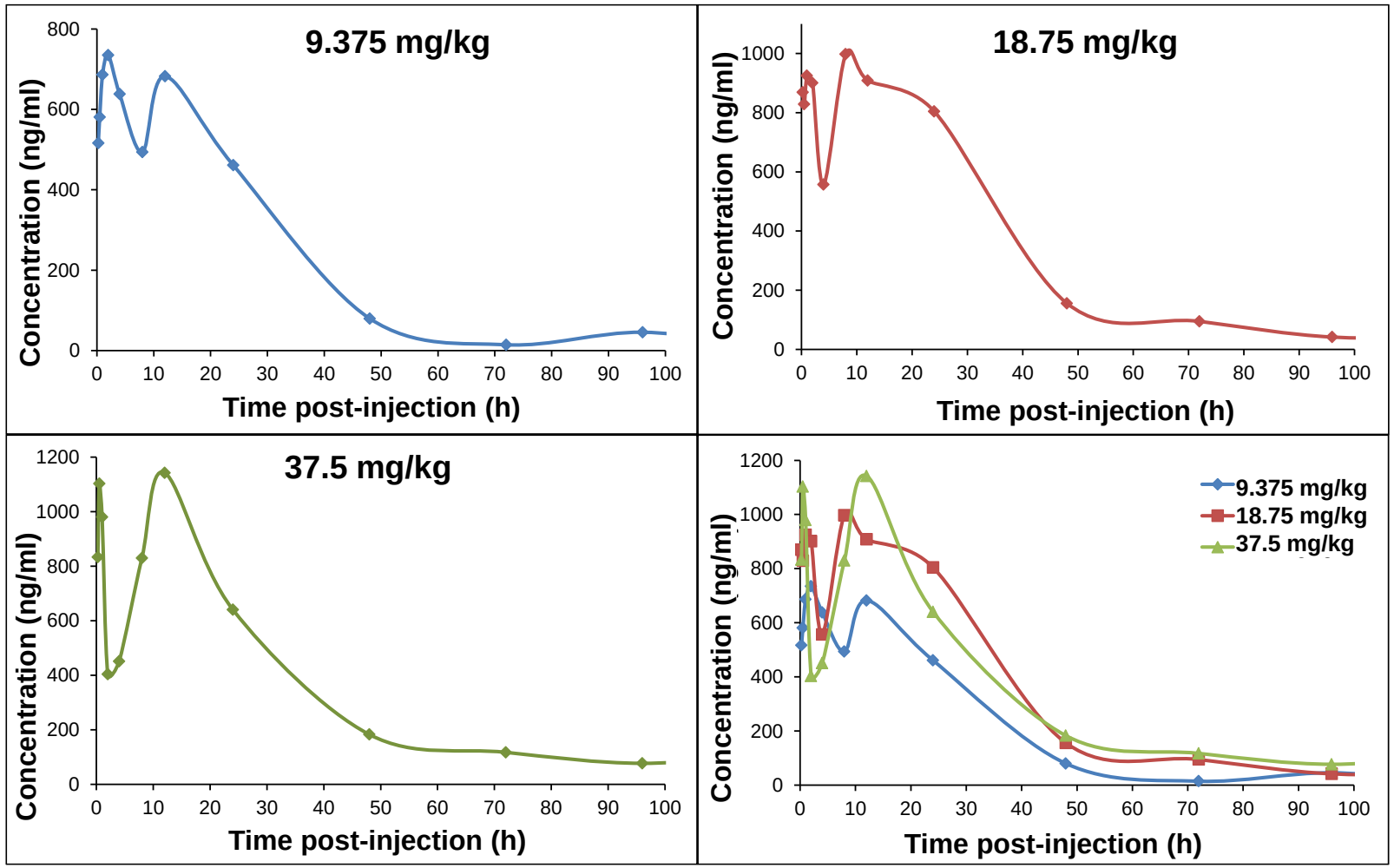
NHP Model: Pharmacokinetics of GT3



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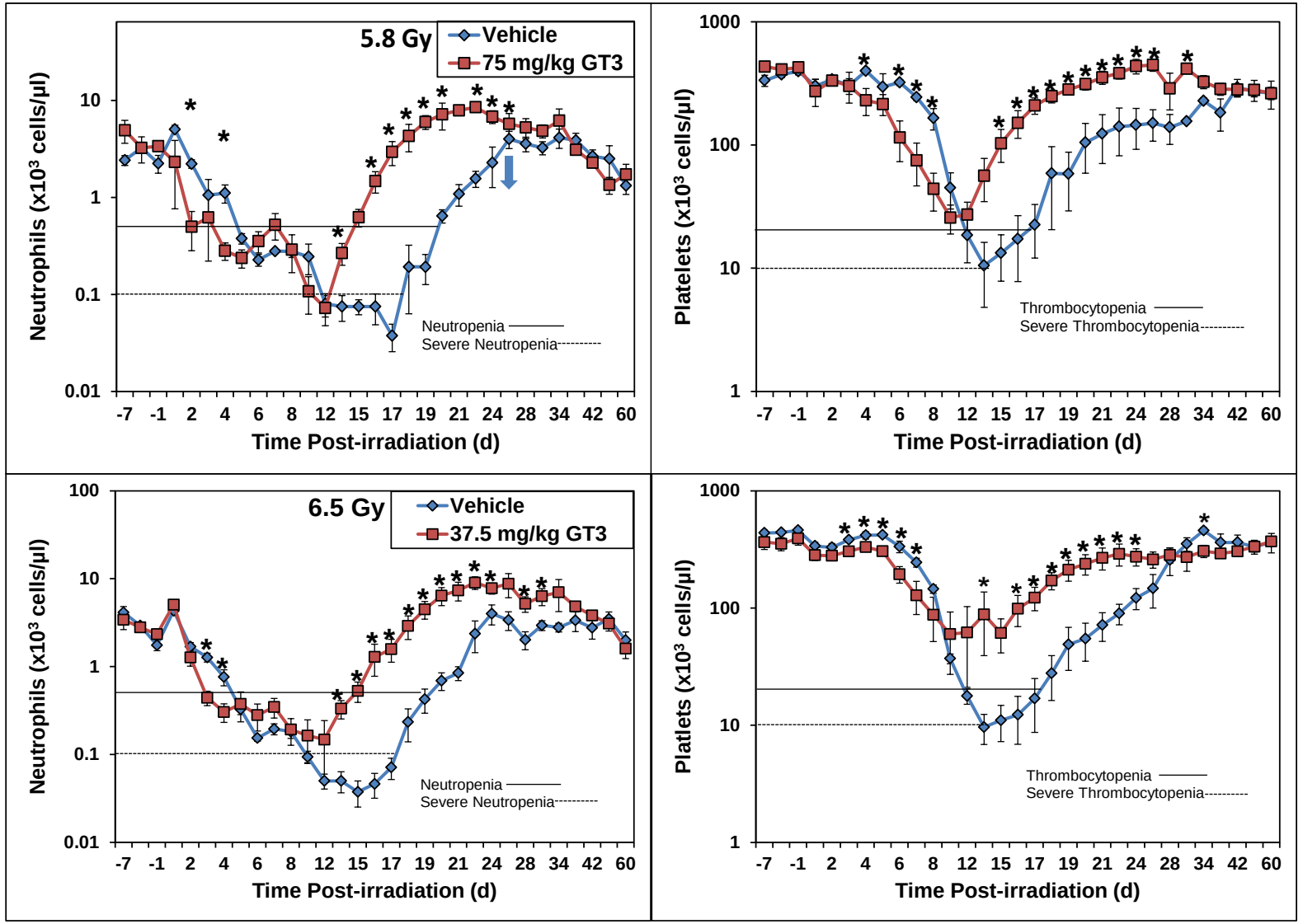
Hematopoietic recovery - GT3 in NHP



Single dose of GT3, No use of blood product, Recovery for both Neutrophils and platelets

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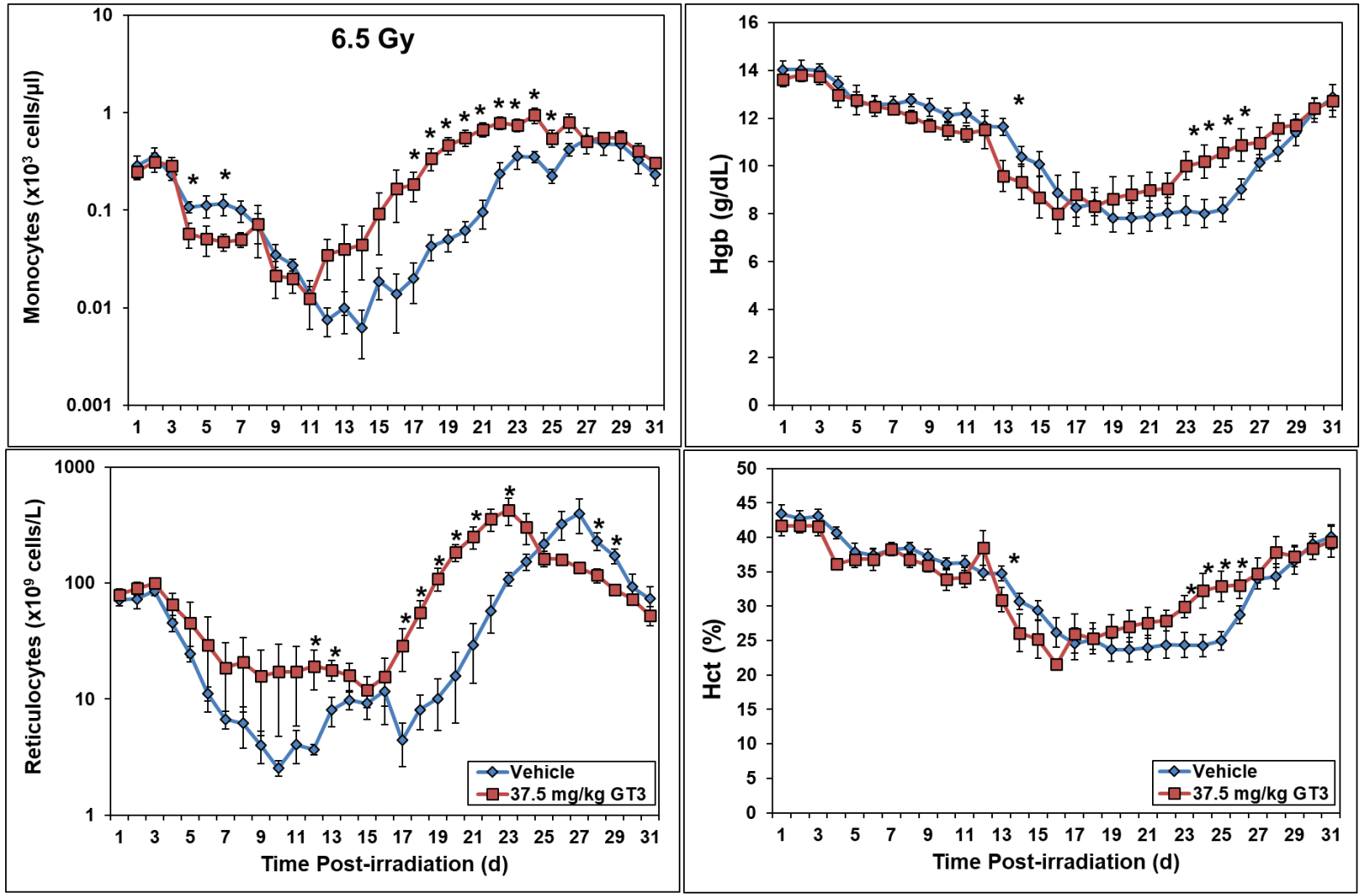
Hematopoietic recovery - GT3 in NHP



Recovery of several cell lineages – uncommon for other MCMs

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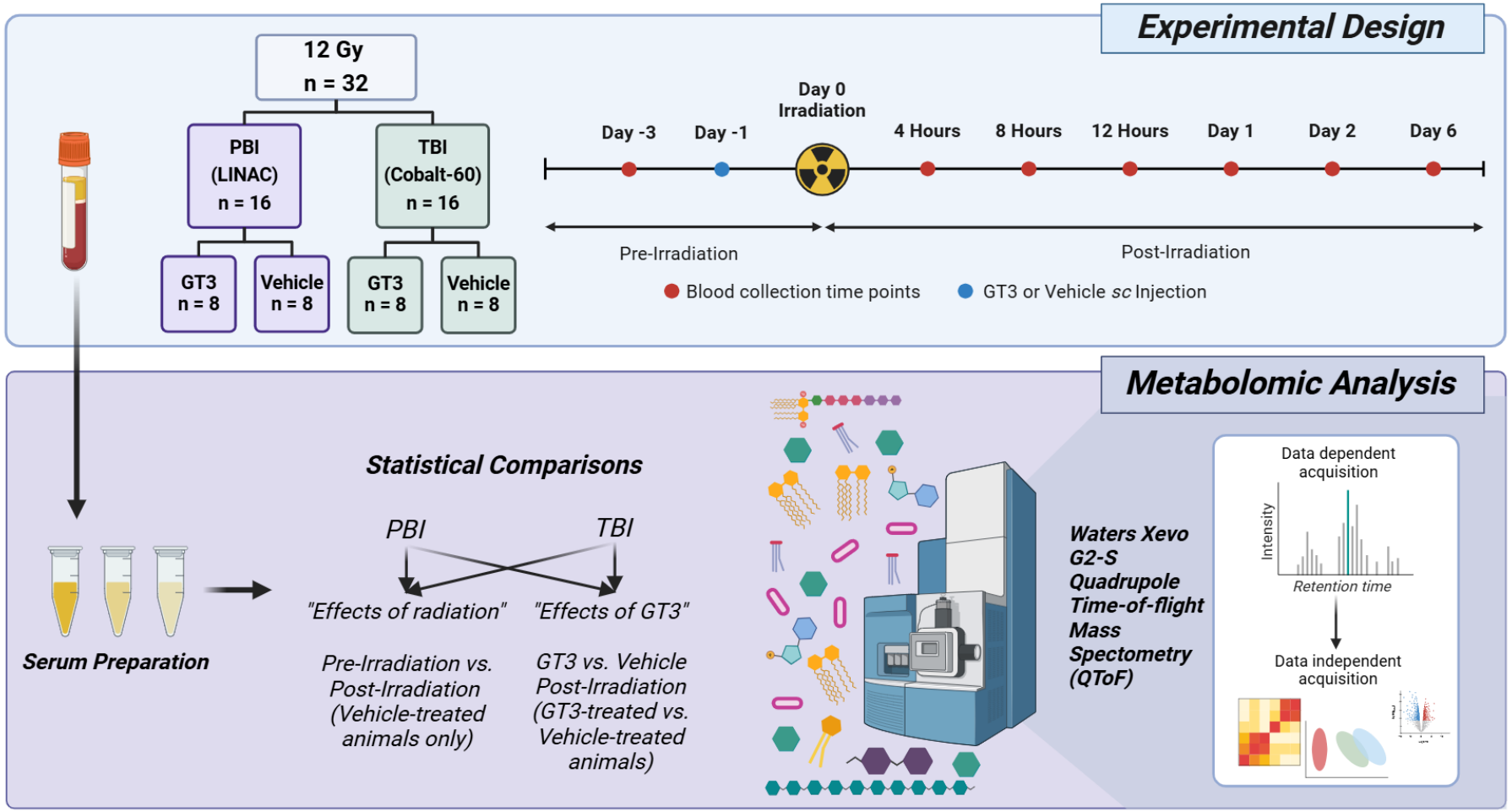
Biomarker Studies: Metabolomics - Experimental design and workflow - 12 Gy serum



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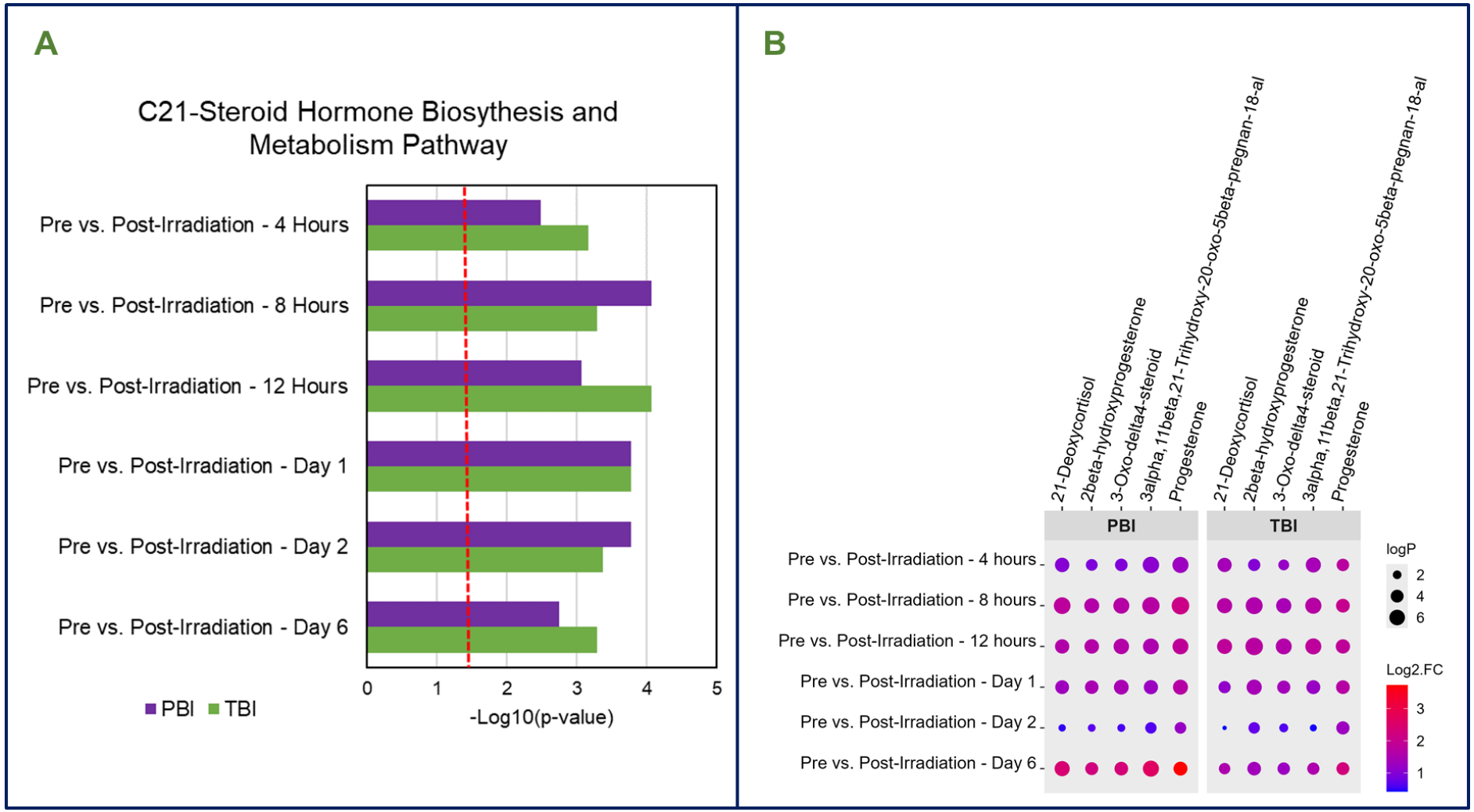
Panel A. Consistent dysregulation to the C-21 steroid hormone biosynthesis, Panel B. Steroid metabolites significantly dysregulated by both PBI and TBI.



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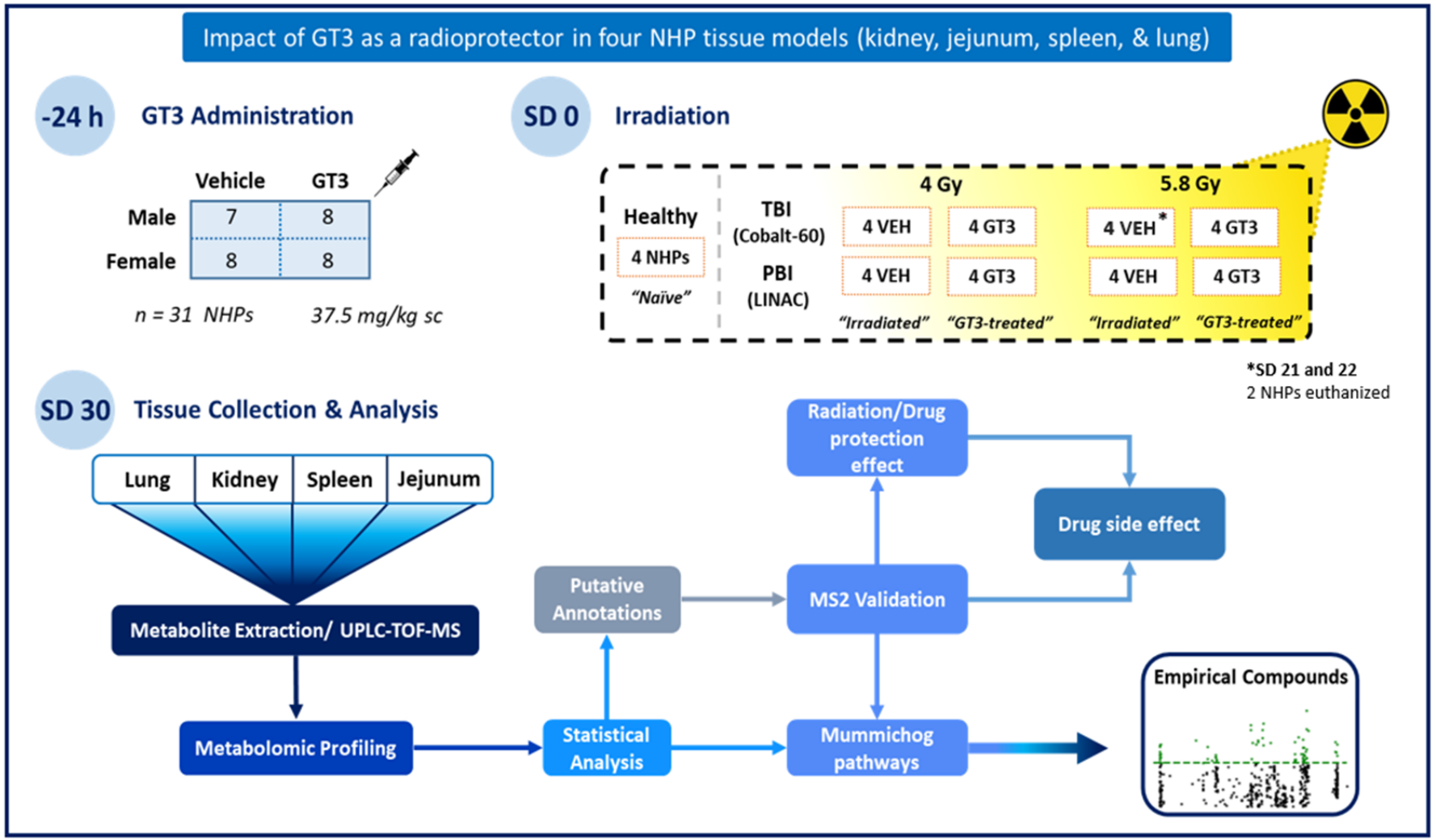
Metabolomic longitudinal effect of GT3 for different radiation types and doses – Tissues 4.0/5.8 Gy



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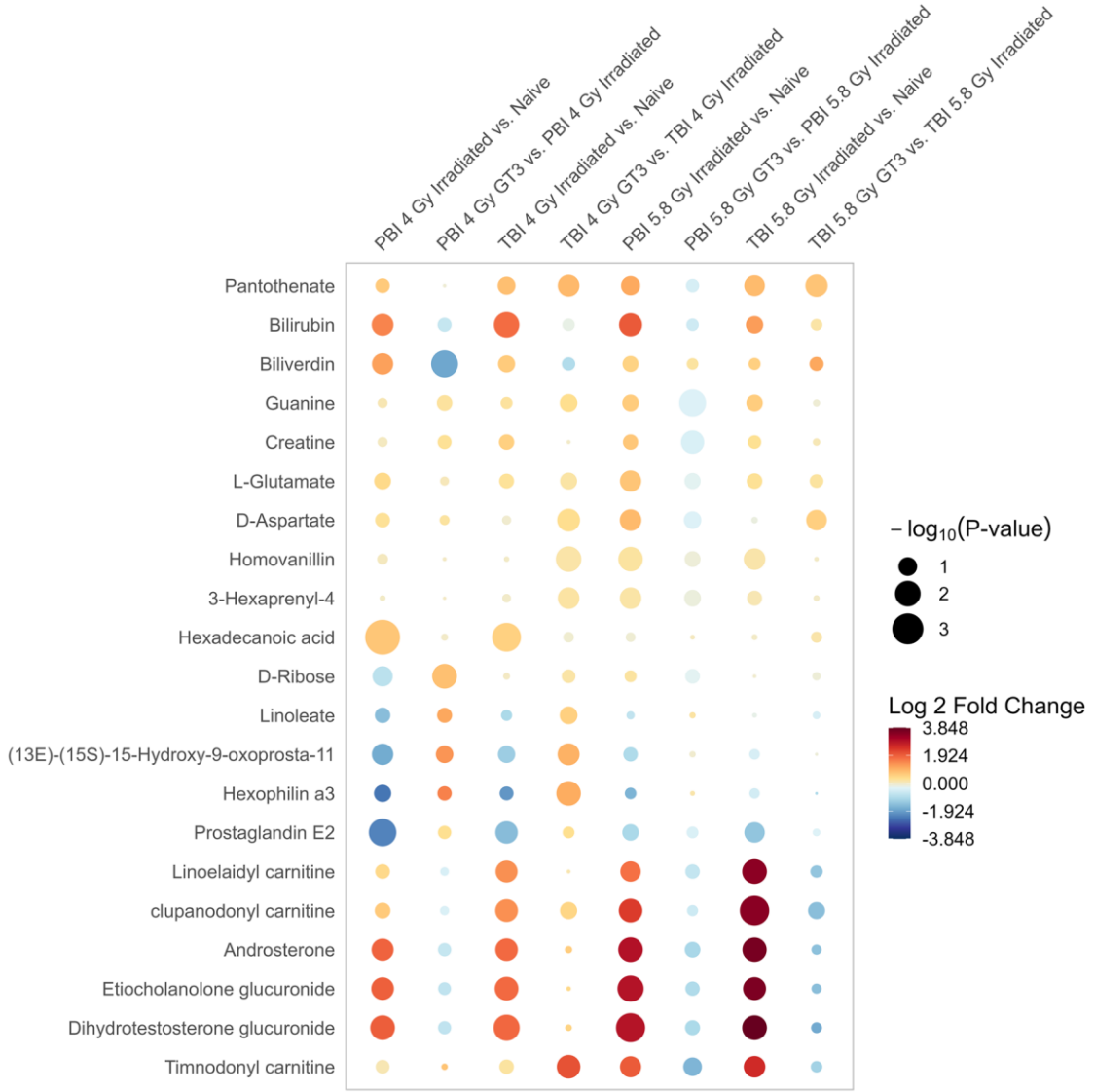
Select metabolites illustrating the effects of radiation and GT3 treatment in lung tissue in each comparison



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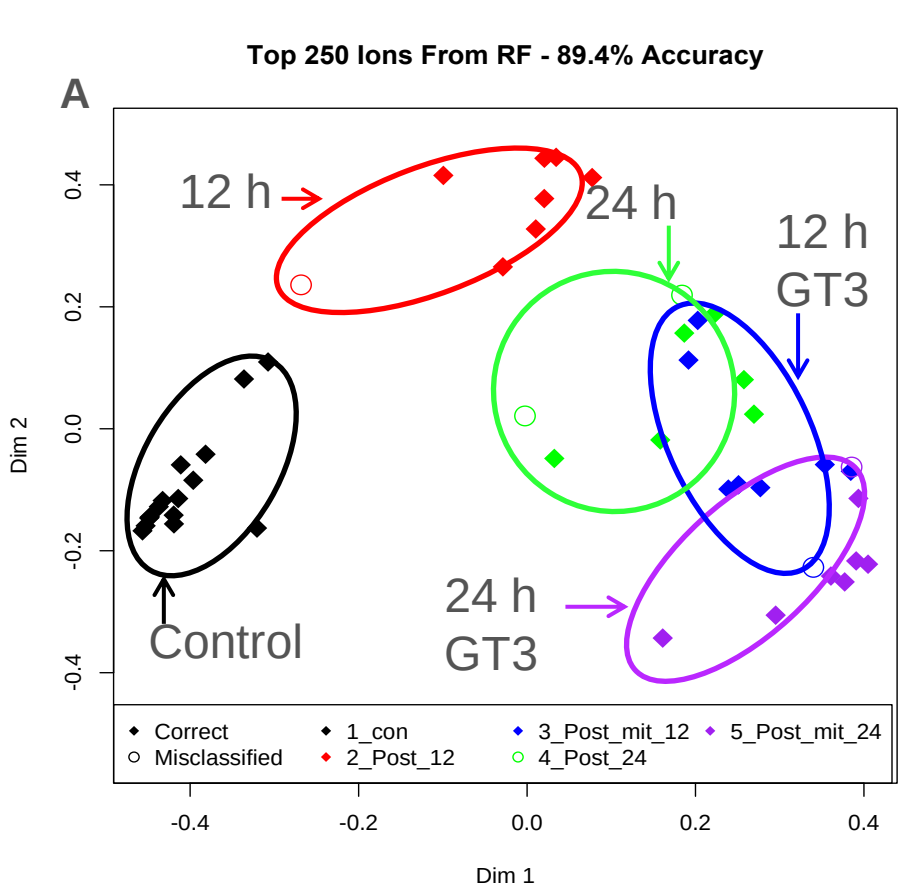
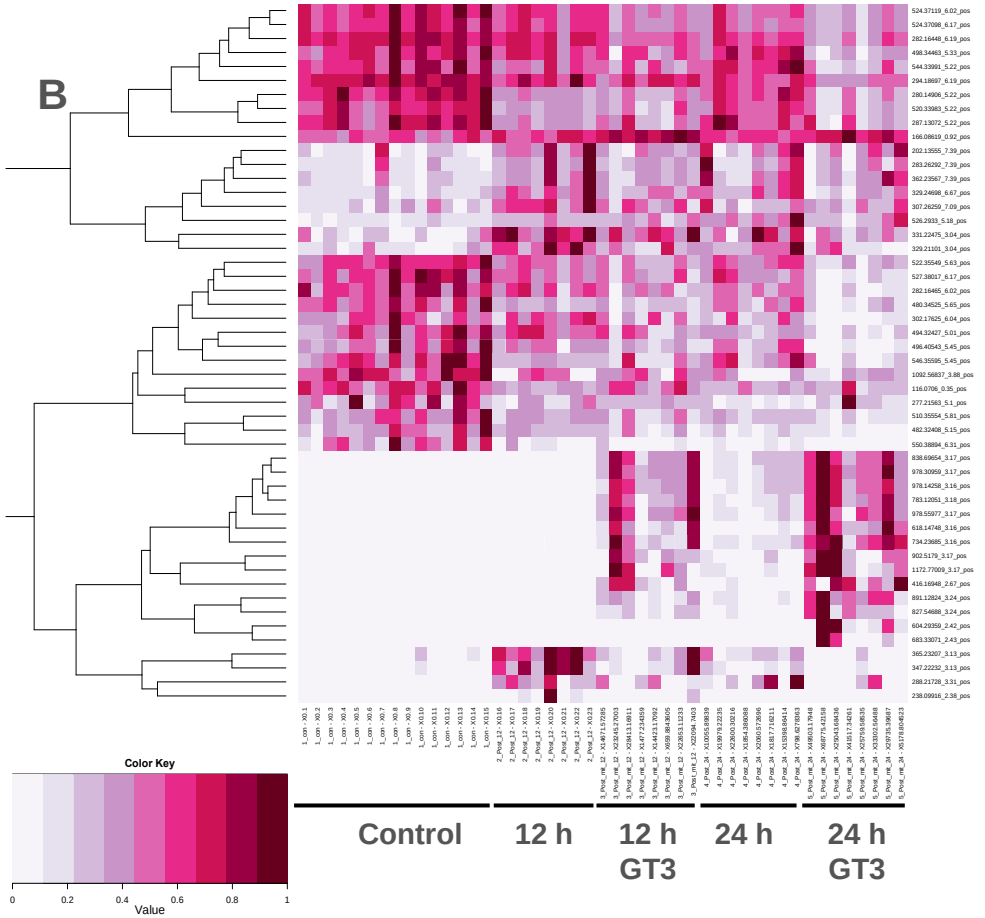
Metabolomics NHP serum 6.5 Gy MDS plot (A) and heatmap (B)





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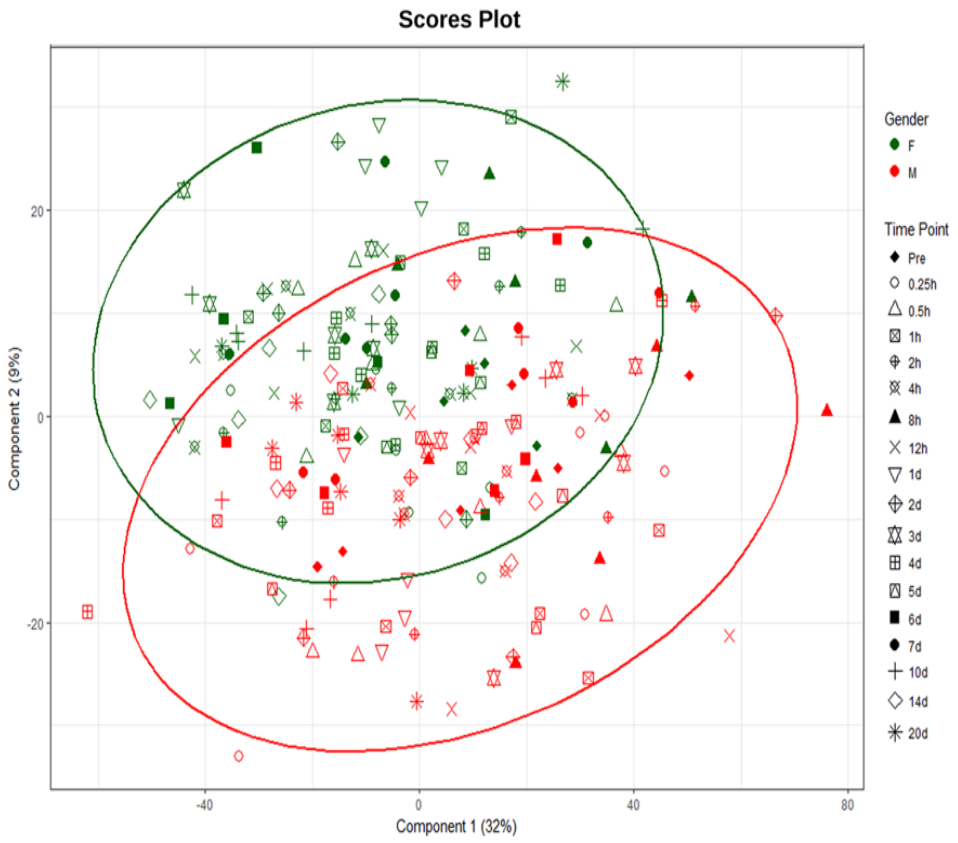
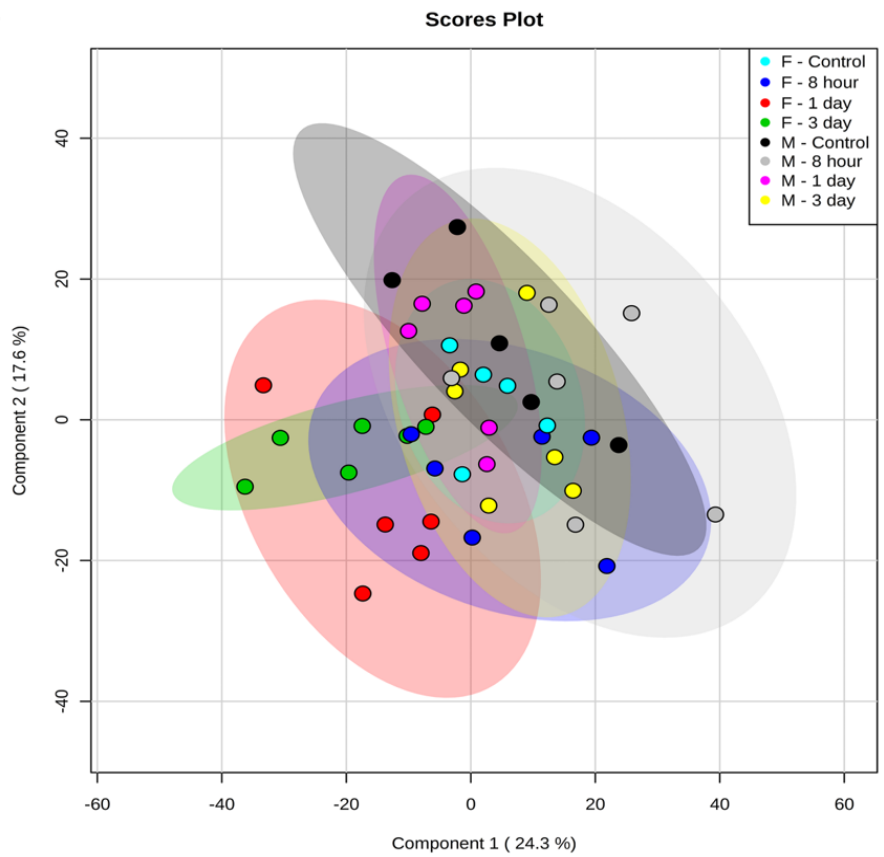
Metabolic profiles (A) across all GT3-treated NHPs, separated by gender and (B) A subset of time points that were shown to have maximal separation against control – No radiation exposure

A



B



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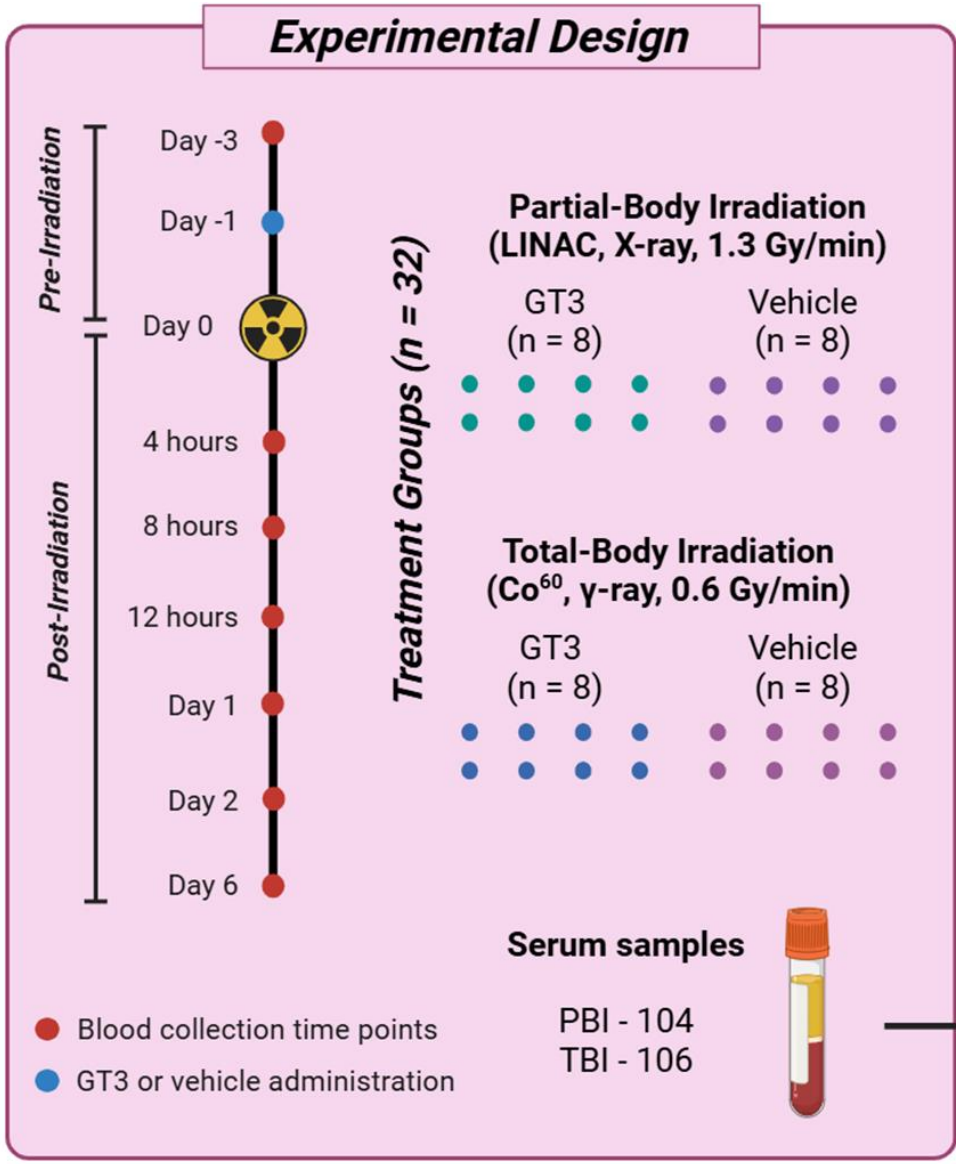
Proteomics schematic experimental design & analysis: 12 Gy serum



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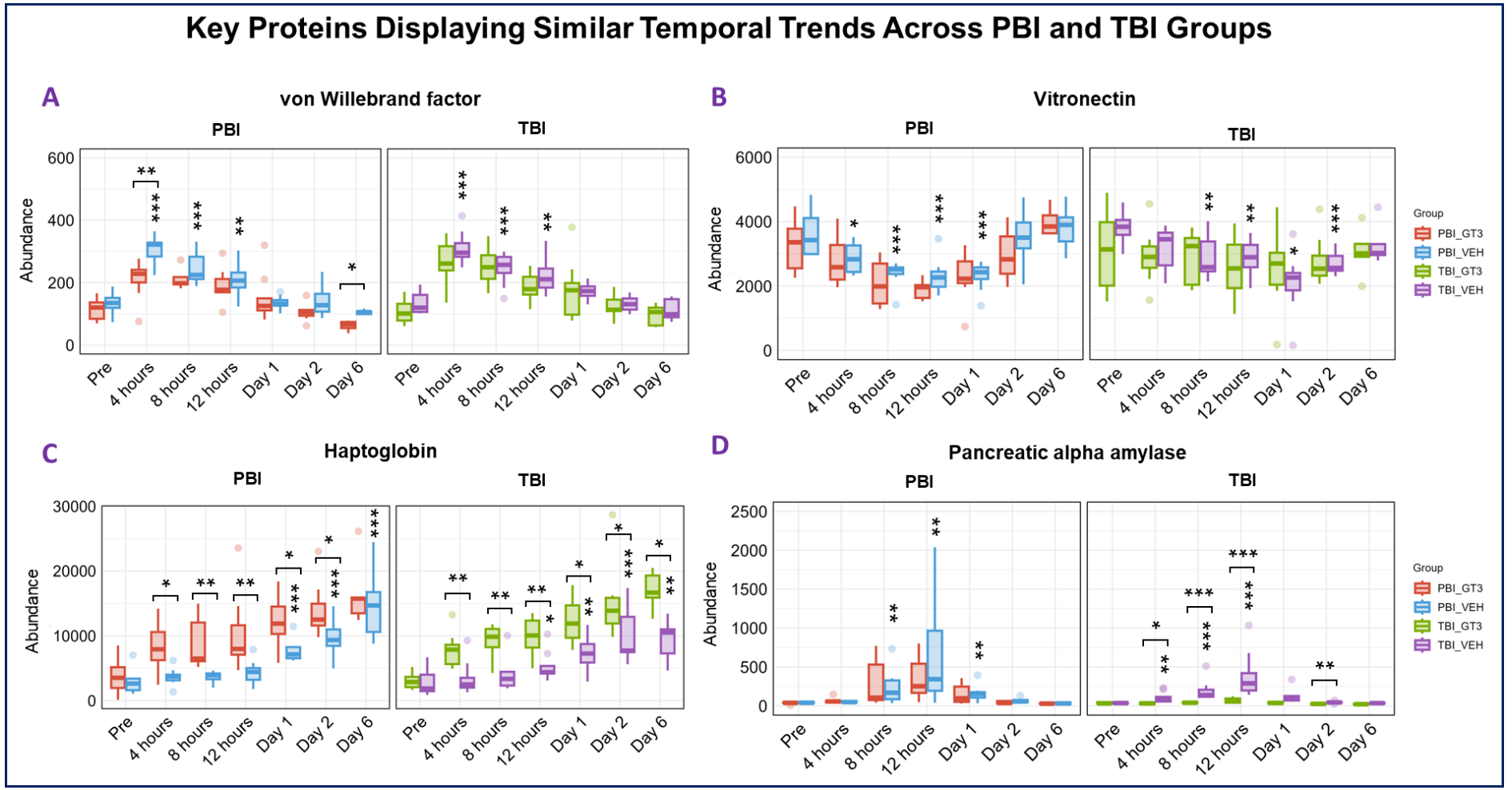
Box plots of proteins that displayed distinct trends over the course of the study



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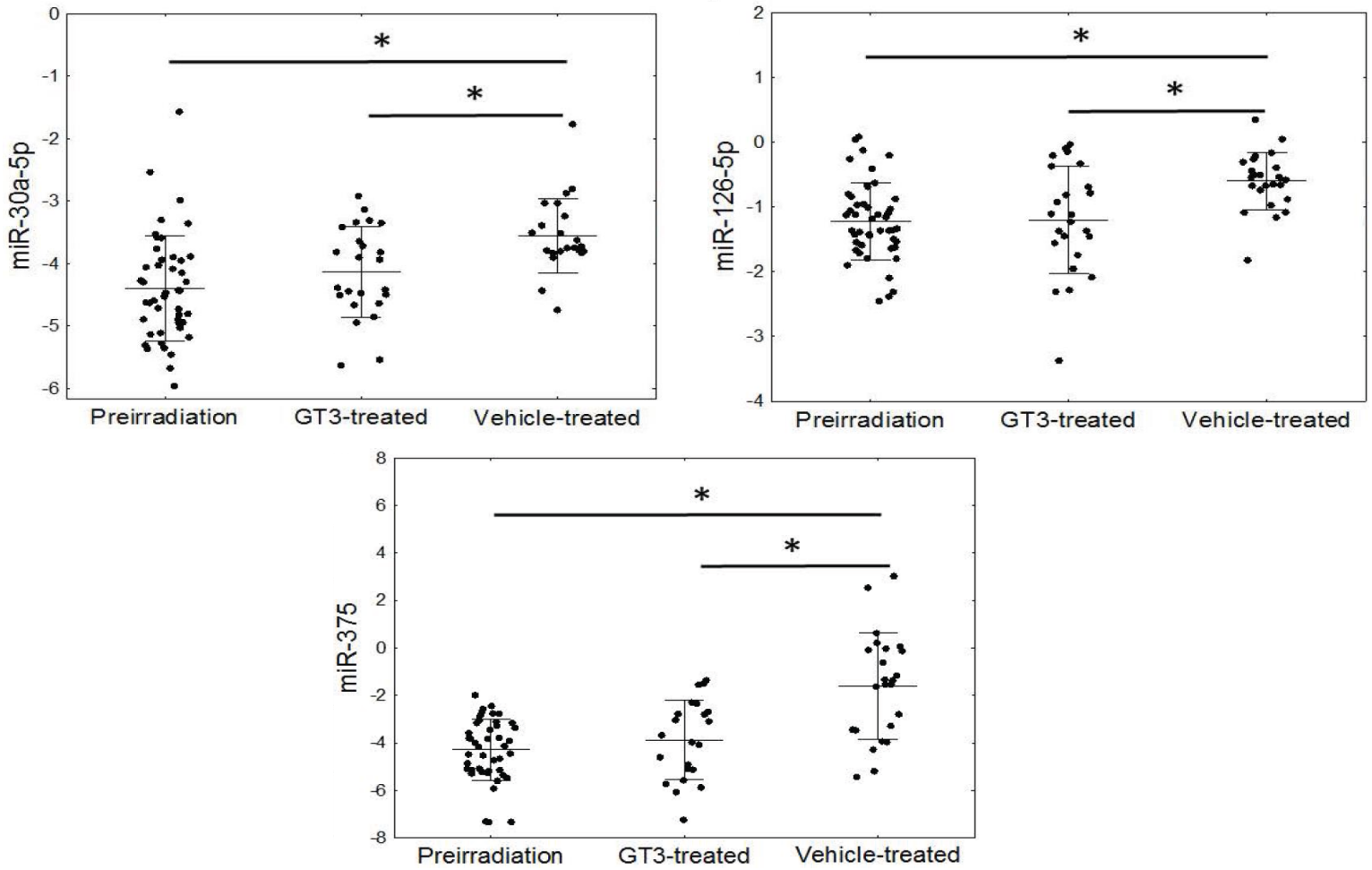
GT3 impact on radiation-dependent miRNA levels in NHPs



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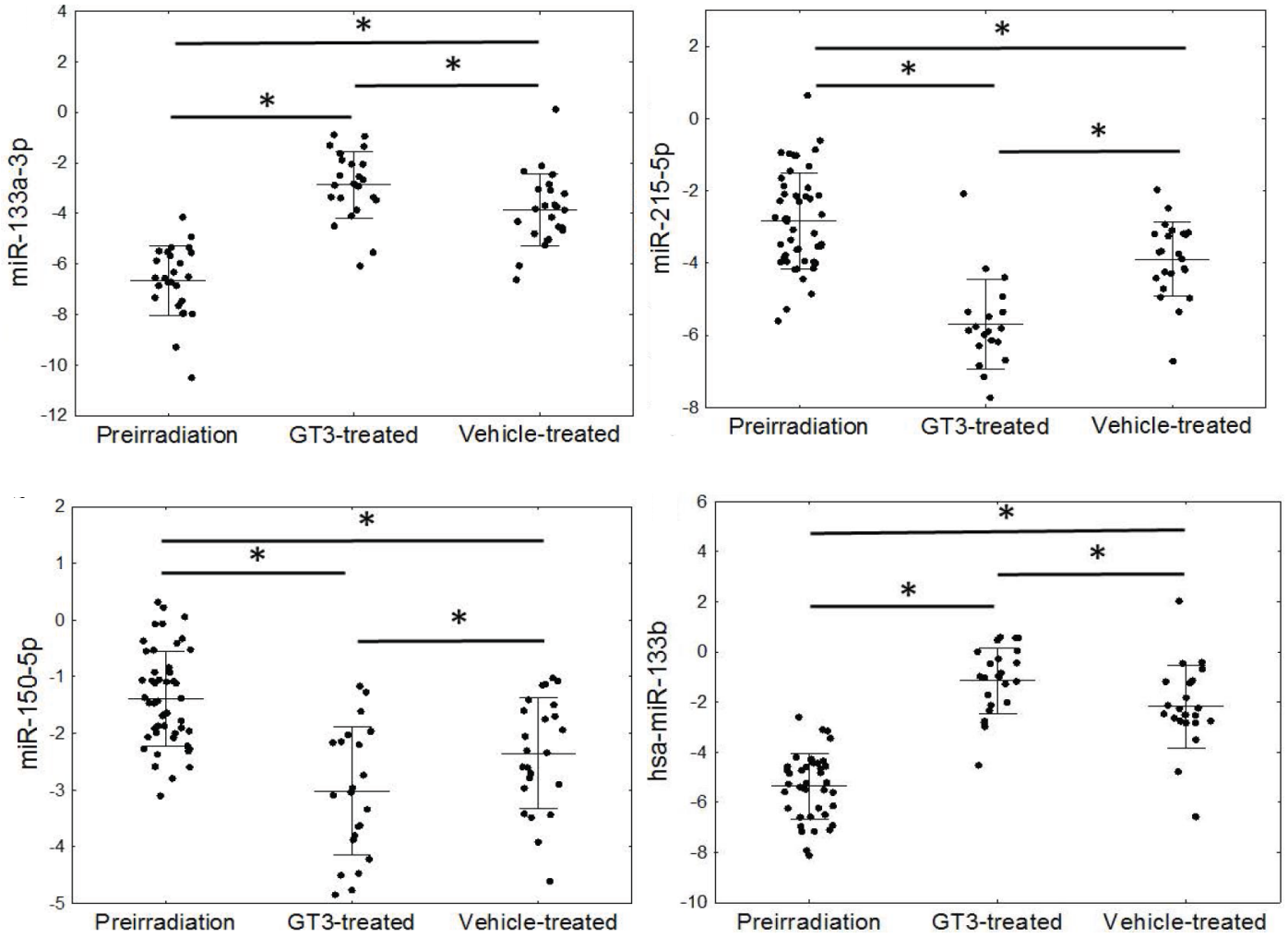
miRNA - Extreme radiation-induced change by GT3 in NHPs



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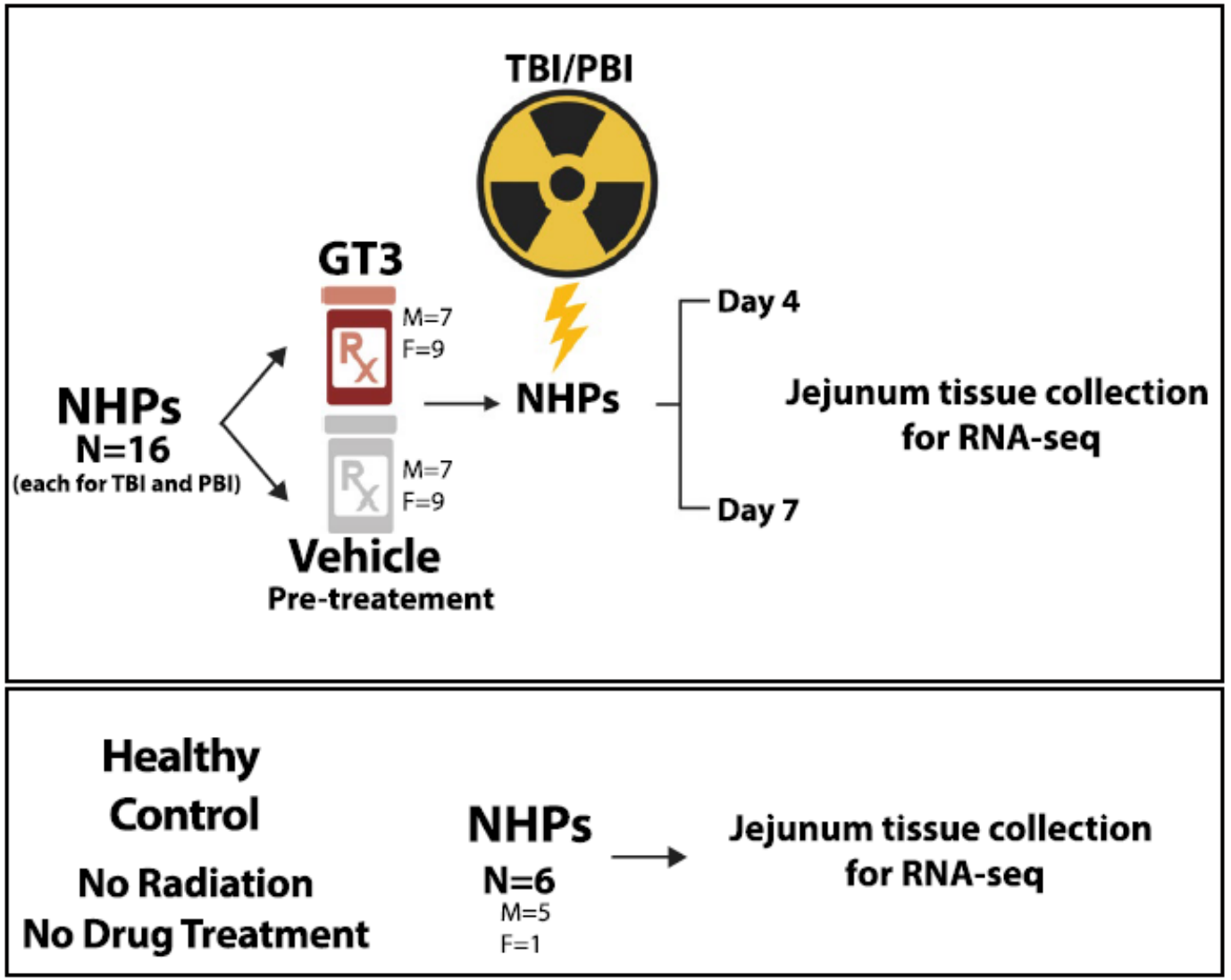
Transcriptomics Study



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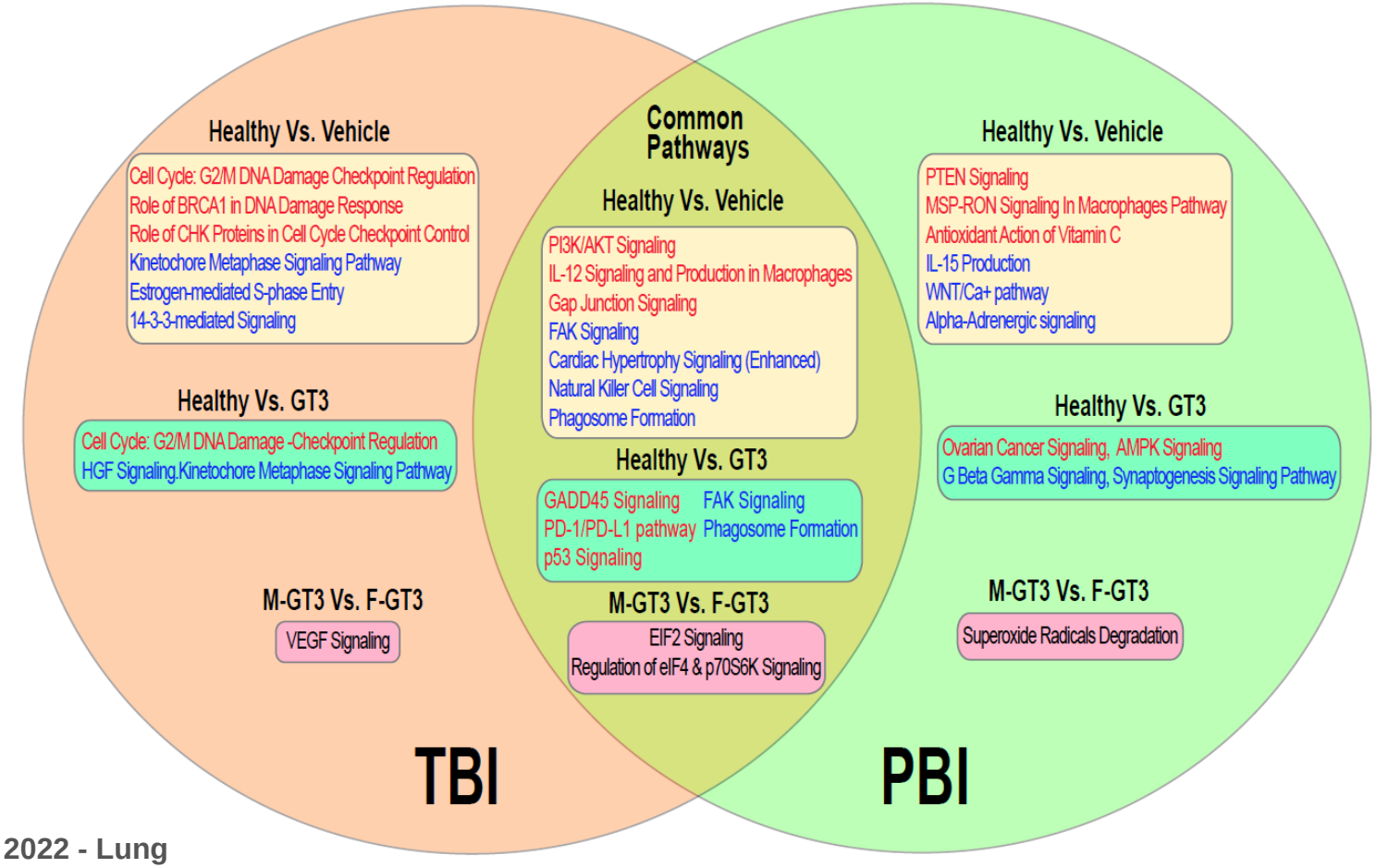
Common and unique pathways identified in different comparisons across TBI and PBI - lung transcriptomics – GT3-treated NHPs – Various organs



Mol Ther Nucleic Acids 29: 310, 2022 - Lung
BMC Genomics 24:274, 2023 - jejunum
Rad Res 205:31-46 2026 - Spleen

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Summary

- **GT3 is a promising radioprotective MCM**
- **Single administration of GT3 without supportive care (blood product) is equivalent, in terms of improving hematopoietic recovery, to multiple doses of approved radiomitigators**
- **Hematopoietic recovery: Several cell lineages - Neutrophil, Platelets, Monocytes, RBC, HGB, HCT, Reticulocytes**
- **Several important biomarkers have been identified: need to be validated across species**
- **There is interest from a Corporate partner to develop it**
- **Few IND enabling studies and NHP efficacy with sufficient *n* are needed.**

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