2.2 Replacing Cesium-137 Irradiators at University of California, Los Angeles

Gamma-irradiators, X-irradiators, and Radiobiology

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The University of California owns (owned) 47 Cesium or Cobalt irradiators

10 campuses and 5 medical centers

Cesium 137
- Research irradiators – 36
- Medical- blood irradiators- 6

Cobalt 60
- Research – 2
- Medical-gamma knives – 3

223,000 staff and faculty
~ 273,000 students

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University of California, Berkeley

NNSA (National Nuclear Security Administration) Incentives

One γ-irradiator removed and replaced with one x-irradiator => $135K

Two γ-irradiators removed and replaced with one x-irradiator => $203K

Three γ-irradiators removed and replaced with one x-irradiator => $216K

Four γ-irradiators removed and replaced with one x-irradiator => $230K

UC President Management Decision

A "**UC Decision Memo**" was written analyzing the scope of the issue for the University and it proposed:

Dedicated Project Management – A dedicated person to manage the program.

Technical Conferences – Hold two conferences to discuss the technical issues of converting from Cesium irradiators to x-ray irradiators.

Faculty Working Group – Form a Faculty Technical Working Group to provide technical recommendations on how to proceed.

Centralized purchasing – Streamline purchasing of the new x-ray irradiators by centralizing the process and seeking best prices.

The plan was endorsed and presented to senior management.

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Campus	Location	Clin/Res	Use	Identifier	Replacement X-irradiator
UCLA	BSRB	Research	Animal	Mark 1-68A	XRAD 320
UCLA	CHS	Research	Animal	GammaCell 40	XRAD 320
UCLA	CHS	Research	Animal	Mark 1-68A	
UCLA	CHS	Research	Cell/Animal	Mark 1-30	
UCLA	CHS	Research	Dosimetry/Animal	T-1000	
UCLA	Rehab Cntr	Research	Cell	GammaCell 10	
UCLA	TLSB	Research	Animal/Cell	Mark 1-68A	RS2000
UCLA	Hospital	Clinical	Blood		One for one
UCLA	Hospital	Clinical	Blood		One for one

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$$\textbf{RBE} = \frac{\text{Dose of Cs-137 } \gamma\text{-rays to produce a given biological effect}}{\text{Dose of x-rays to produce the same biological effect}}$$

x-ray energy	RBE to CS-137	Relative dose increase	system	endpoint	citation	notes	Model
320 kV (1mm Cu HVL)		1.16	Bone marrow	Clonogenic growth post in vivo IR	Belley et al. 2015		animals
320 V (4mm Cu HVL)		1.07	Bone marrow	Clonogenic growth post in vivo IR	Belley et al. 2015		animals
320 kV	0.763		Splenocytes TBI	cytotoxicity	Scott et al. 2013		animals
320 kV	1.346		Bone marrow TBI	cytotoxicity	Scott et al. 2013		animals
160 kV	See note		Bone marrow	Bone marrow transplant reconstitution	Gibson et al. 2015	Due to the statistically significant variability in B, T, myeloid cell reconstitution between the X-ray and 137Cs sources of irradiation, we accept the null hypothesis. We conclude that although both sources were efficient at ablating endogenous bone marrow sufficiently to enable stem cell engraftment, there are distinct physiologic responses that should be considered prior to choosing the optimal source for use in a study. In addition, irradiation using the 137Cs source was associated with lower overall morbidity.	animals
300 kV (1.65mm Cu HVL)	1.11		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 100 cells/circumference ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.08		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 10 cells/circumference for ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.07		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 1 cells/circumference for ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.00		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 100 cells/circumference for a single fraction of 11.36 Gy	animals
300 kV (1.65mm Cu HVL)	1.00		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 10 cells/circumference for a single fraction of 11.36 Gy	animals
300 kV (1.65mm Cu HVL)	1.08		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 1 cells/circumference for a single fraction of 11.36 Gy	animals
320 kV (HVL 1mm Cu)	1.5		HBEC-13	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 1mm Cu)	1.6		HBEC-2	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 3.7mm Cu)	1.2		HeLa	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 3.7mm Cu)	1.5		A549	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
300 kV (HVL 3mm Cu)	Approx 1.23		C57BL/6	LD50/30	UCLA radonc		animals

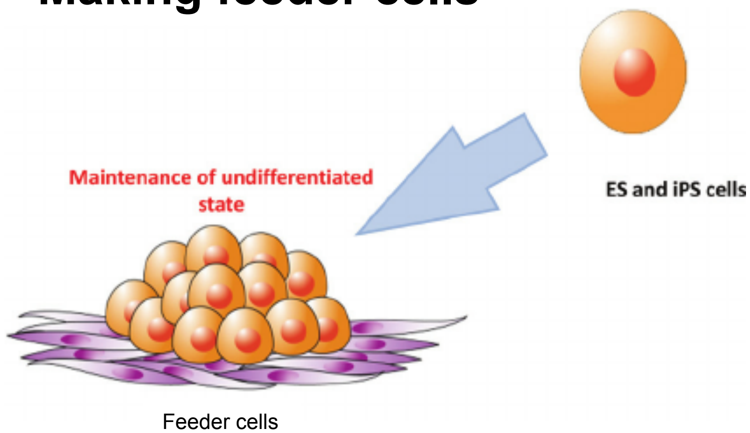
UC-wide Survey Results

Approximately half the studies involve *in vitro* (cells) and half involve *in vivo* (rodents) irradiations.

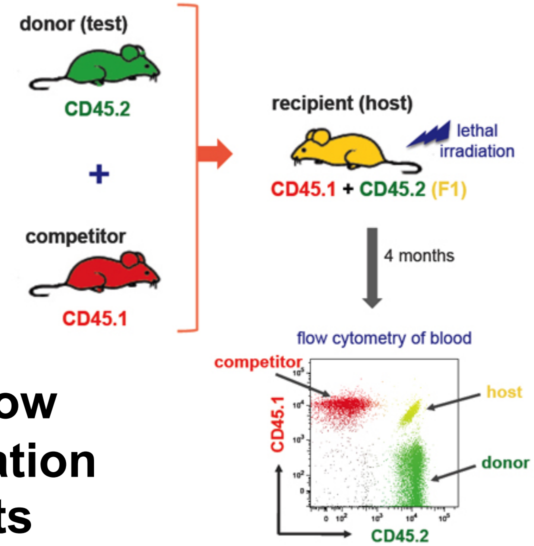
The largest single proportion (41%) of the *in vitro* irradiations was for production of feeder cells to support growth of growth-factor-dependent cells.

The largest single proportion (37%) of the *in vivo* irradiations was for bone marrow ablation in preparation for transplantation experiments.

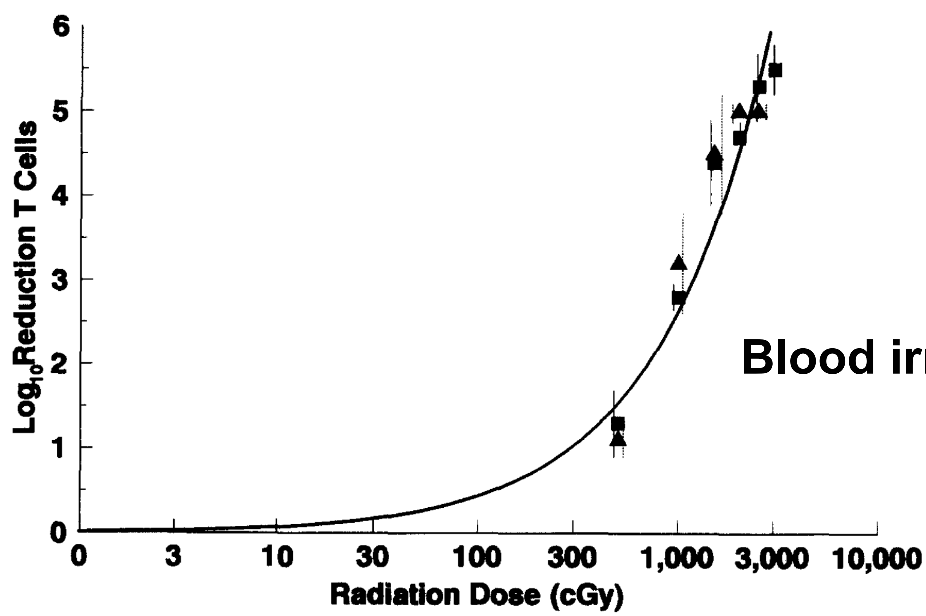
Making feeder cells



Bersenev 2011

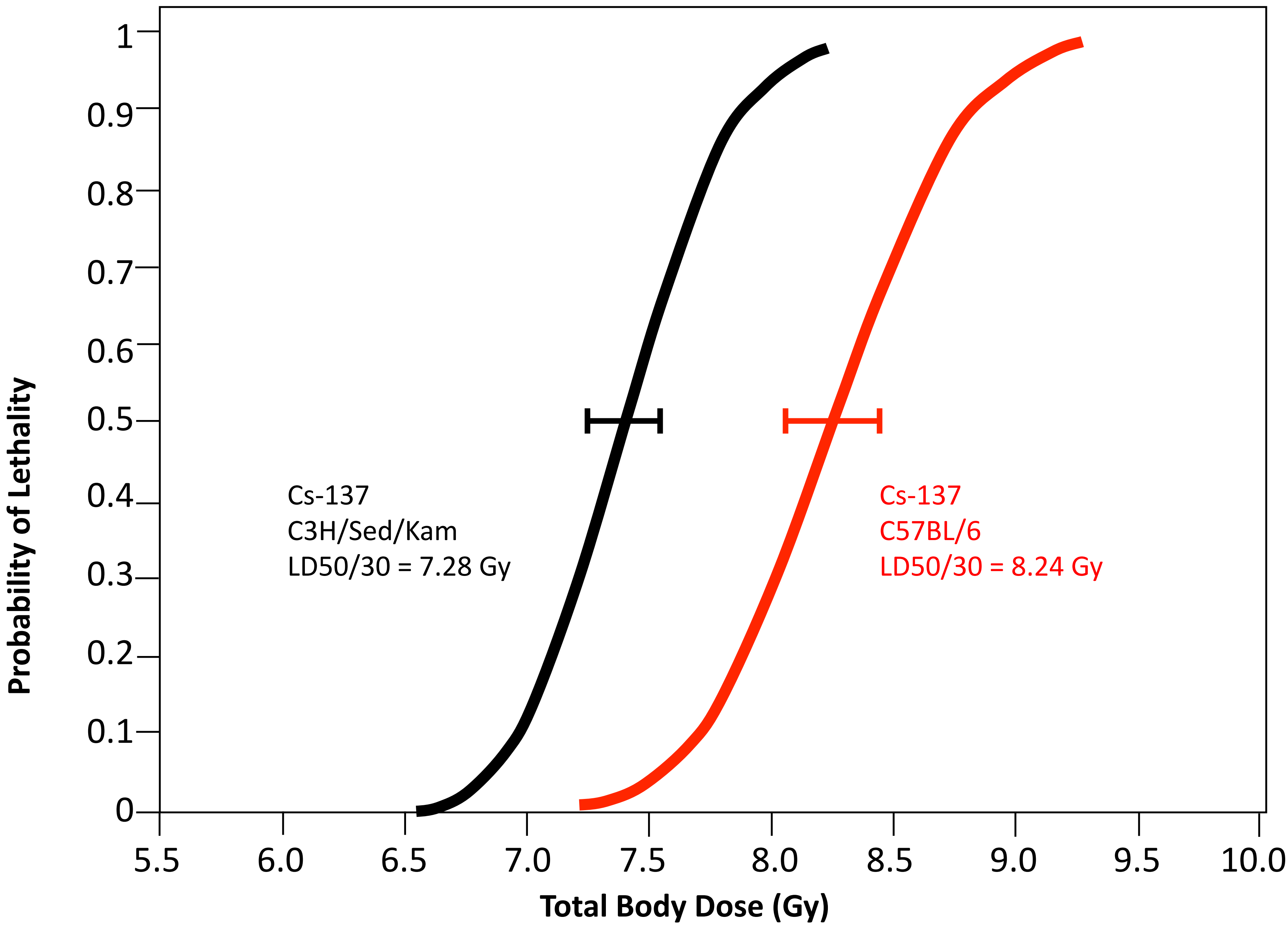


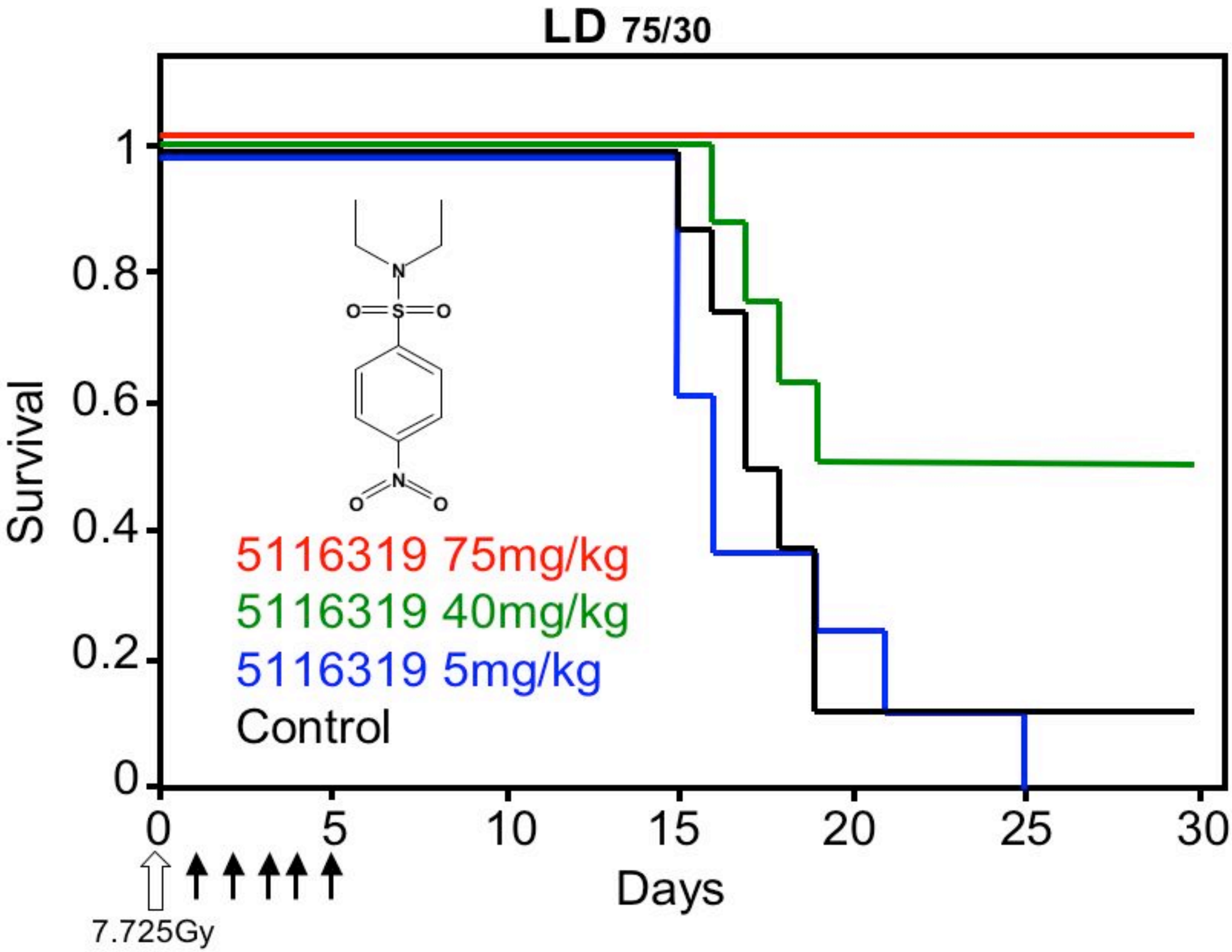
Bone marrow transplantation experiments

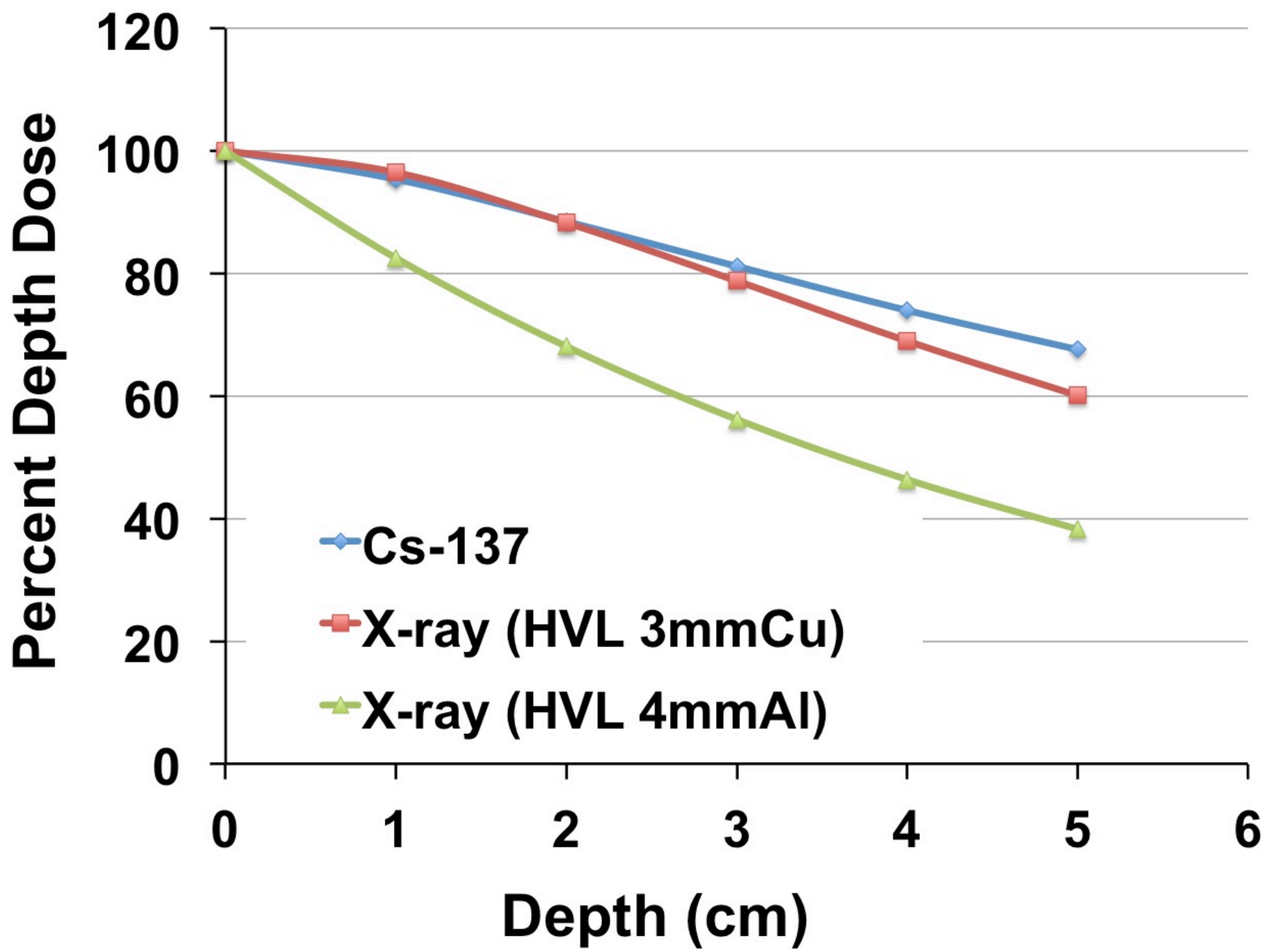


Blood irradiations to prevent GVHD

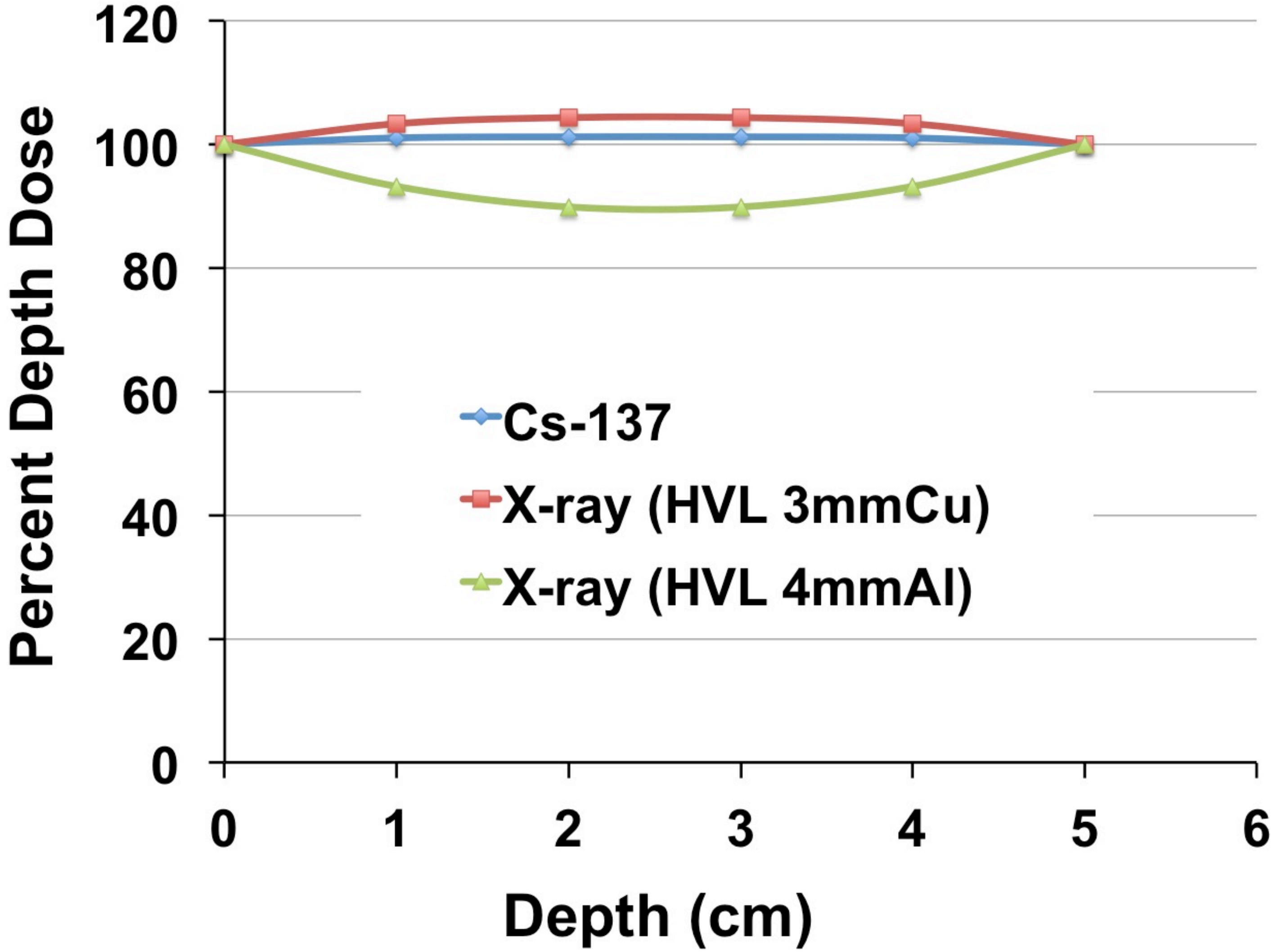
Pelszynski, et al. 1994

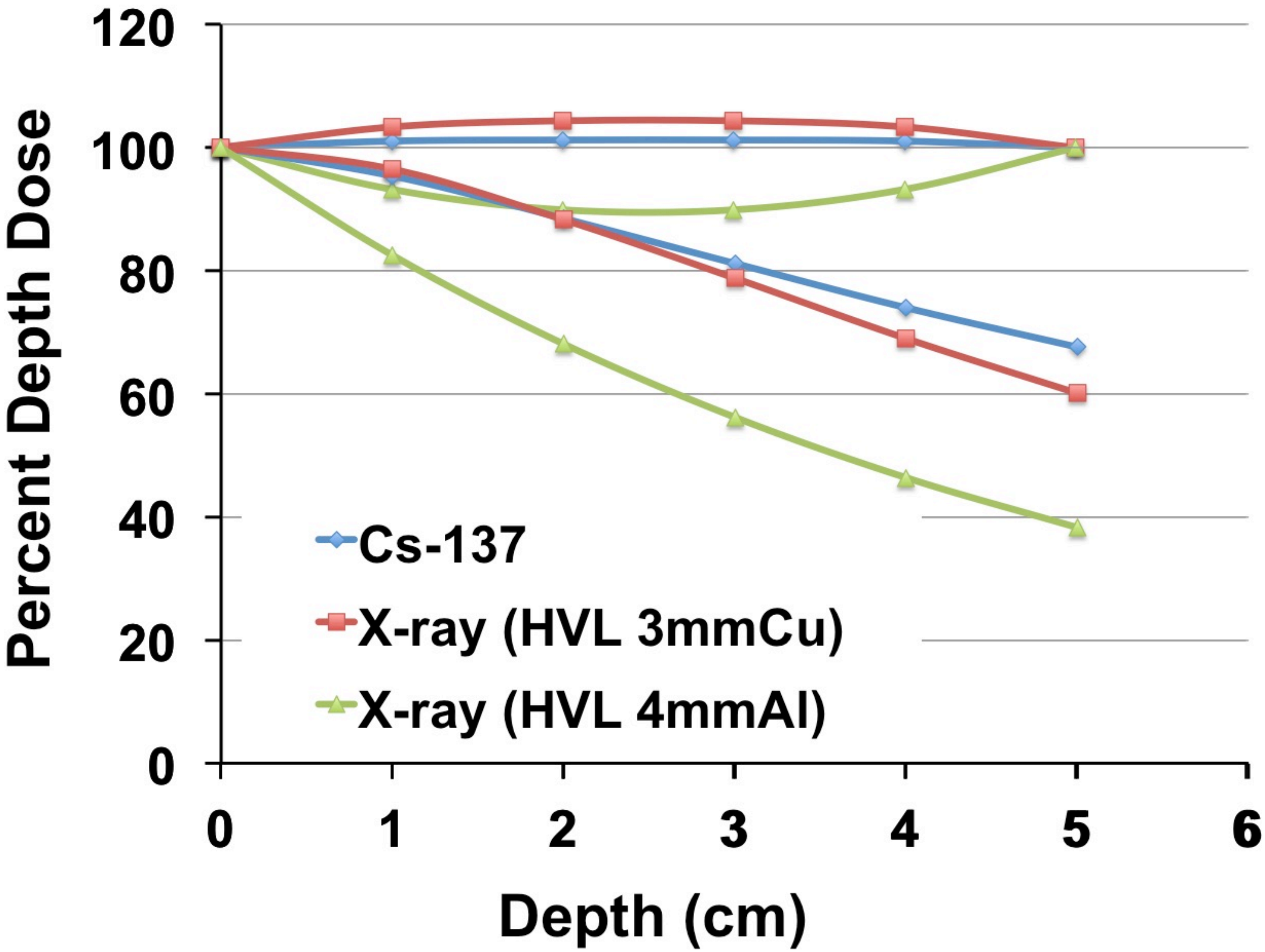

Probability of Lethality
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
Total Body Dose (Gy)
Cs-137
C3H/Sed/Kam
LD50/30 = 7.28 Gy
Cs-137
C57BL/6
LD50/30 = 8.24 Gy


LD 75/30
1
0.8
0.6
0.4
0.2
0
Survival
N
O
S
O
N
O
O
5116319 75mg/kg
5116319 40mg/kg
5116319 5mg/kg
Control
0
5
10
15
20
25
30
Days
7.725Gy



Percent Depth Dose
120
100
80
60
40
20
0
0
1
2
3
4
5
6
Depth (cm)
Cs-137
X-ray (HVL 3mmCu)
X-ray (HVL 4mmAl)


120
100
80
60
40
20
0
Percent Depth Dose
0
1
2
3
4
5
6
Depth (cm)
Cs-137
X-ray (HVL 3mmCu)
X-ray (HVL 4mmAl)


120
100
80
60
40
20
0
Percent Depth Dose
0
1
2
3
4
5
6
Depth (cm)
Cs-137
X-ray (HVL 3mmCu)
X-ray (HVL 4mmAl)

Radiobiological Considerations or Not

- **Biology is a dynamic system**
  There is always a response

- **Biological dose ≠ physical dose**
  In general, x-rays (energies equal to or below 320 kV) are more biologically effective than Cs-137 gamma rays suggesting that lower doses of x-rays will be required to achieve the same biological endpoint as Cs-137 gamma rays. Conversely, less penetration in some targets may reduce dose effects.

- **Different endpoints => different RBE's**
  It is difficult to provide a simple conversion factor for equating x-ray effects to Cs-137 effects because RBE depends on multiple factors including x-ray peak energy, x-ray energy spectrum (filtration), biological system, endpoint, etc.

- **Different IR sources & conditions => different cellular responses**
  Standardization – Unlike the single gamma energy of Cs-irradiators, output energies of the x-irradiators cited in the literature are diverse due to variations in x-ray tubes and filtration utilized; in some cases, the quality of the beam (HVL) is not described.

  Geometry can make a difference

- **ID of the IR may not matter much or at all in some cases**
  Each experiment will need to be individually calibrated when converting from Cs-irradiators to x-irradiators and the effort and resources required will depend on the precision of the effect desired. For example, in cases where inactivation of support cell proliferation or unwanted cell activity is desired, as in the case of production of feeders, the specificity of the absolute dose may not be as critical as ascertaining animal lethality dose.

UC Source Replacement Faculty Working Group (WG)

Recommendations:

- **X-ray irradiators can replace cesium irradiators in many applications**. There are likely some exceptions though, such as the need for very high radiation doses or radiation exposures over a period of days, and research specifically requiring high energy gamma radiation.
- **Every established laboratory/investigator needs to empirically assess the effects to their studies** of converting from cesium to x-rays specific with their **own comparison studies.**

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Lessons Learned for a Smooth Transition

A collaborative approach is best! Do not force researchers to switch – make them a part of the decision making process.

Offer money incentives, options to upgrade research equipment and support for comparison studies.

Talk to the researchers about their research – do not shut down research but plan for exceptions.

Take a phased approach- acceptance will come with time.

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