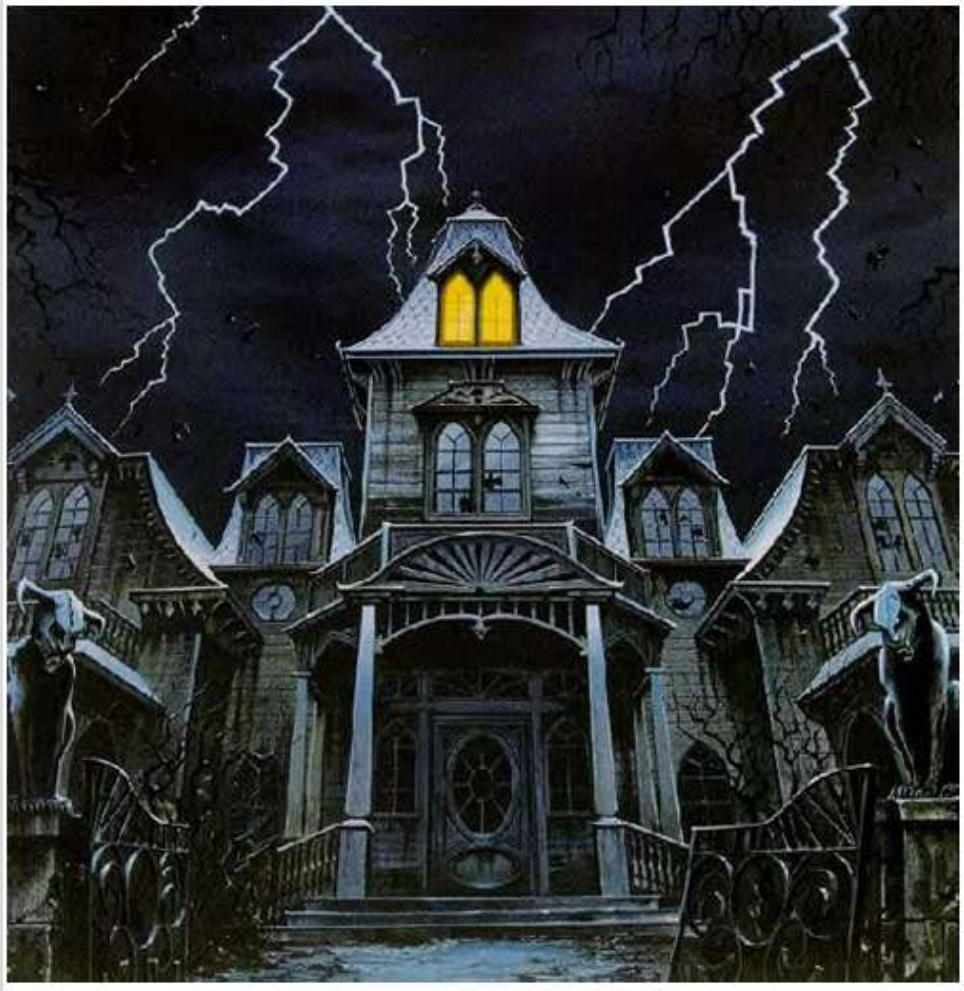
Large-Animal Radiation Dosimetry



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Not as scary as you think!

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Radiation Dosimetry and Biology

- “It’s all about decreasing the uncertainties”.
  - Consider the uncertainties in delivering and measuring a dose of radiation to a certain tissue depth in Rhesus macaques.
  - THEN
  - Consider the uncertainties in the biological response of the target organ or the whole animal.

Rule #1: Nothing is easy

The Propagation of Uncertainties

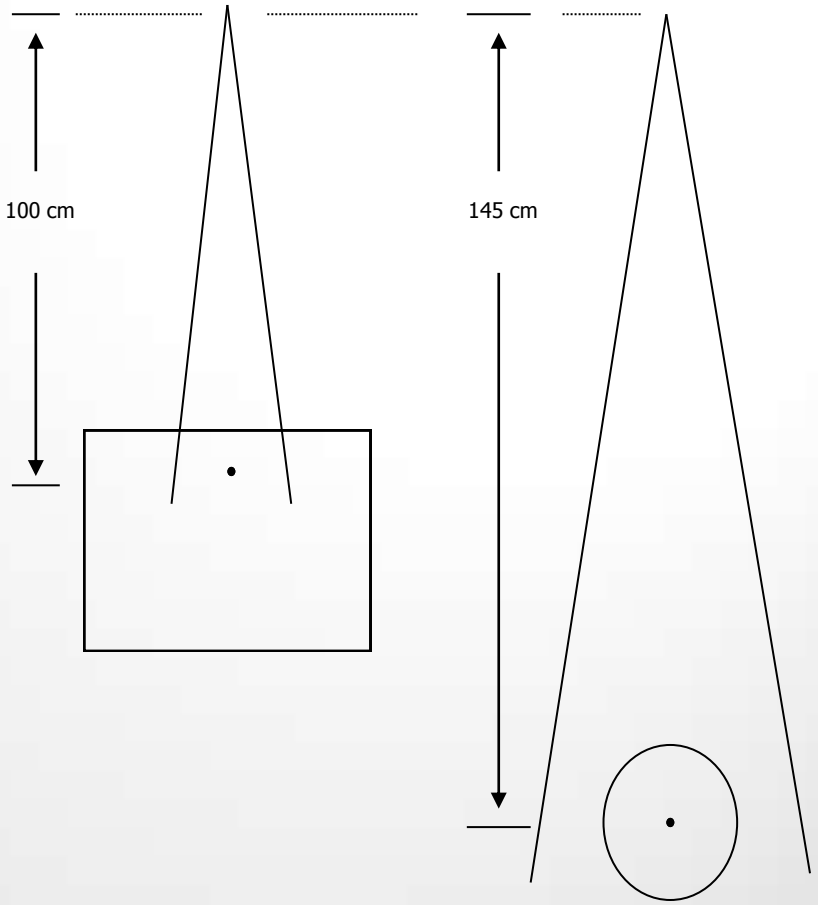
- There are uncertainties inherent in the dose measurement and calculation process
- Estimates of these uncertainties (for animal irradiations) are:
  - Calibration factors of instruments: ~±1-2% (^{60}Co and above), ~±5%$^{+}$ (kV x ray)
  - Accuracy of dose-calculation data: ~±2-5%
  - Precision of measurements in field: ~±5-10%
  - Total uncertainty: From ~±5.0% to ~±10.0% (at one sigma!)
- Uncertainties strongly depend upon the type and energy of the irradiators, the accuracy and thoroughness of the calibration, and the level of radiation physics support that is provided

Initial Commissioning and Calibration: Summary

- Acquire / validate fundamental (relative) dosimetry data
  - Percent Depth Dose (PDD)/ Tissue Phantom Ratios (TPR)
  - Output Factors (OF)
  - Beam Profiles (OAR)
- Confirm concordance with clinical data
- Perform absolute calibration
  - Standard clinical-dosimetry configuration
- Transfer calibration to animal irradiation configuration and validate
  - Measurements / calculations

Transfer of Calibration: Maryland

- Perform calibration in standard configuration
  - Per AAPM TG-51
- Transfer calibration to animal-irradiation geometry using calibration system and suitable phantom
  - Per AAPM TG-29
- Verify calibration in animal-irradiation geometry using clinical dosimetry formalism
- (See next slide)



Initial Commissioning and Calibration: Maryland Unit

- Varian C-Series Accelerator
  - 6 MV X-Ray Beam, 2MV avg.
- PDDs, OFs, OARs match clinical data
- Standard calibration
  - At d_{max}, 100-cm isocenter, 10x10 field
  - Using AAPM TG-51 Protocol
- Transfer calibration to animal-irradiation geometry
  - At 145-cm distance, 40x40 field
  - Use suitable phantom (cylindrical, water-filled, 12-cm diameter, 40-cm long, accepts farmer chamber)
  - Using AAPM TG-29
  - Verify via calculations using standard (Khan) formalism:

$$D = MU \times S_C \times S_P \times S_S \times TMR \times ISq \times OAF$$

(S_s is a geometry factor per TG-29)

Ongoing Quality Assurance

- Follow (essentially) AAPM TG-142
- Determine at time of calibration “constancy checks”
  - Daily Constancy Checks
    - Mechanical checks: lasers, field-size and distance indicators and readouts, field light, safety checks
    - Output and energy check at some standard geometry
    - Calibration of In-Vivo dosimeters (OSLDs)
  - Monthly Constancy Checks
    - Different instrumentation than daily instruments
    - All of the above + flatness and symmetry, light vs. radiation field congruence
  - Annual Checks
    - Full calibration

In-Vivo Dosimetry

- Each and every irradiation
- Verification that all has gone according to plan
  - Reality check
- At Maryland:
  - Optically-Stimulated Luminescent Dosimeters (OSLDs)
    - Landauer MicroStar
  - Entrance and exit dosimeters
    - For TBIs: 2 dosimeters, AP and PA, at xiphoid process.

Radiation Dosimetry and Biology

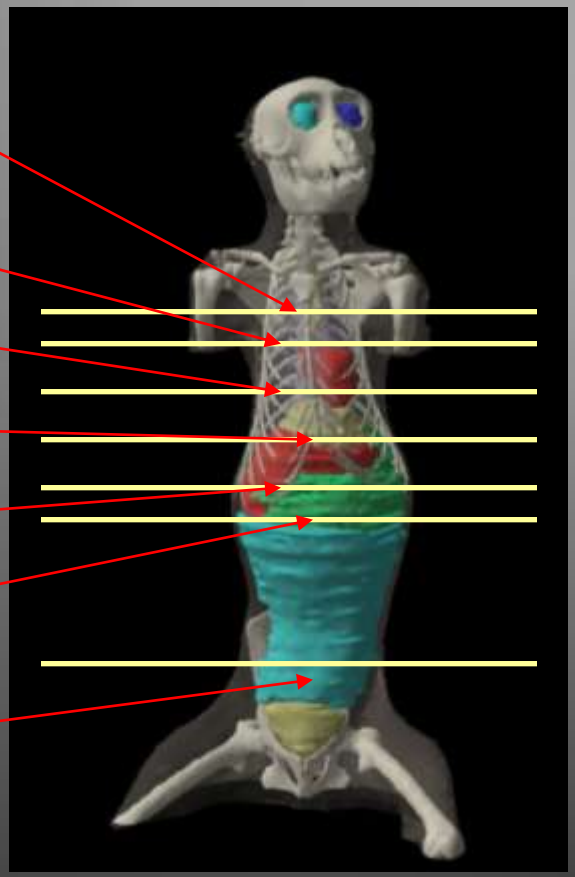
- GLP-Compliant Animal Model Research Platform: The rhesus macaque
  - Males, bw 4.0-11.0 kg; Chinese bred
  - Viral free: SIV, herpes-B etc.
  - MLTD: xiphoid process
  - Dose rate: 0.70-0.80Gy/min
  - Models: Endpoint: Mortality vs Dose over Time
  - TBI: H-ARS 7.0-9.0Gy; GI-ARS 9.0-13.0Gy
  - WTLI: whole thorax lung irradiation, 9.0-12.5Gy
  - PBI/BM5: 9.0-12.5Gy
- Organ-specific injury vs multi-organ injury

Radiation Dosimetry and Biology
Validated Models for Determining MCM Efficacy
FDA-AR

- Recent studies performed in the rhesus macaque
  - TBI: H-ARS dose range, d60, n=48
  - TBI: GI-ARS dose range, d8-15, n=61
  - PBI/BM5: GI-ARS dose range, d8-15, n=74
  - PBI/BM5: GI-, H-ARS + GI prolonged-ARS, d60, n=72
  - PBI/BM5: GI-, H-, GIpro-ARS, + lung-DEARE, d180, n=64
  - WTLI: lung-DEARE, 180d in-life

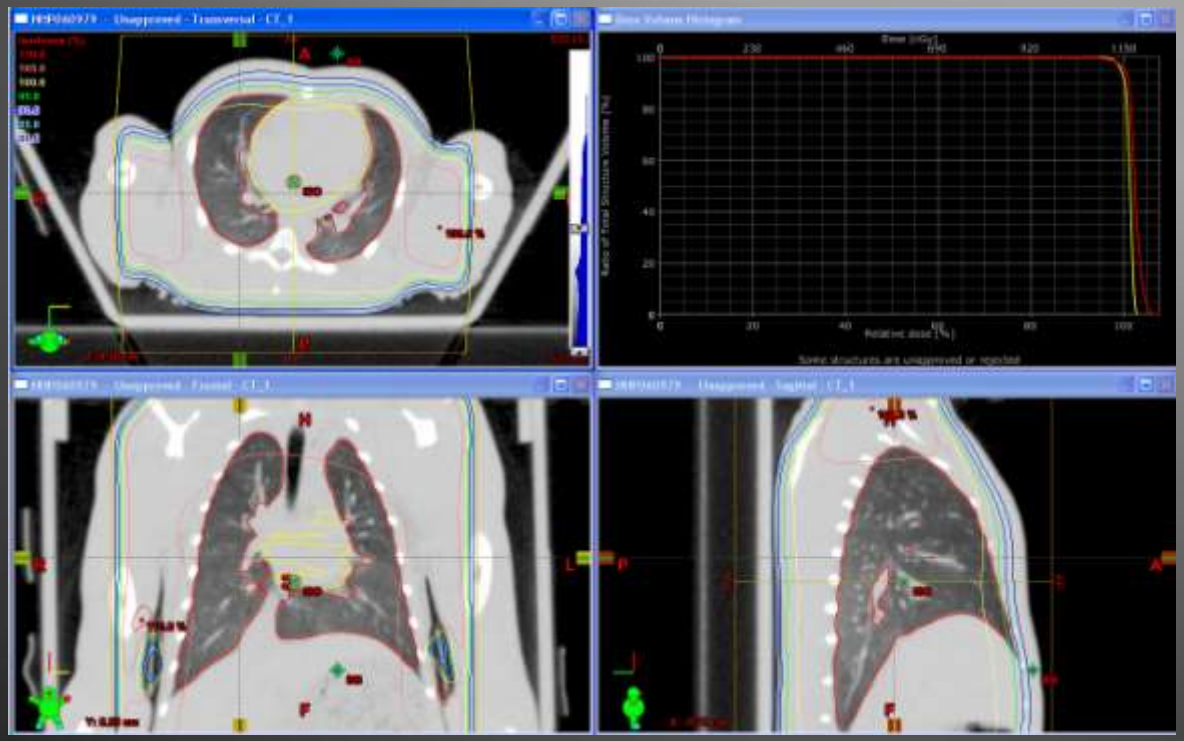
Cross sectional images

- Upper lung lobe
- Middle lung
- Lower lung
- Stomach/Liver
- Liver/colon
- Colon bowel
- Bowel/pelvis



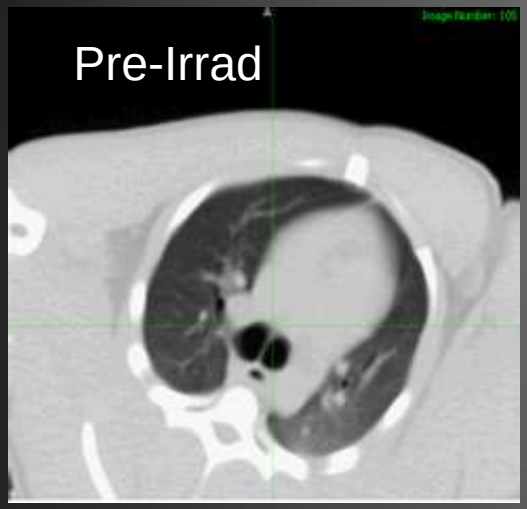
WTLI Dose Distribution

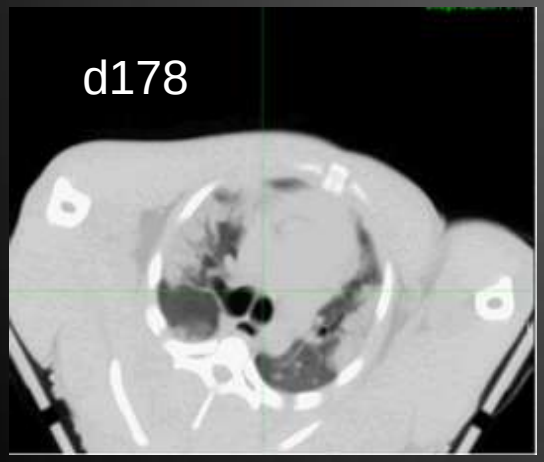
- Dose calculation to “midplane”
- Relatively uniform but not all structures receive an equal dose



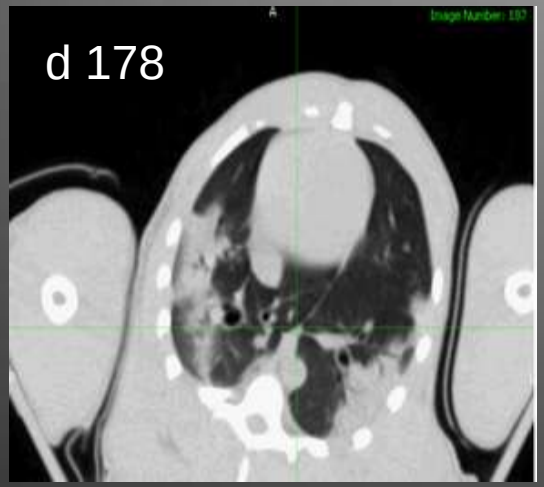
CT Scans of NHPs

NHP R03007 10Gy
5%BM Shield

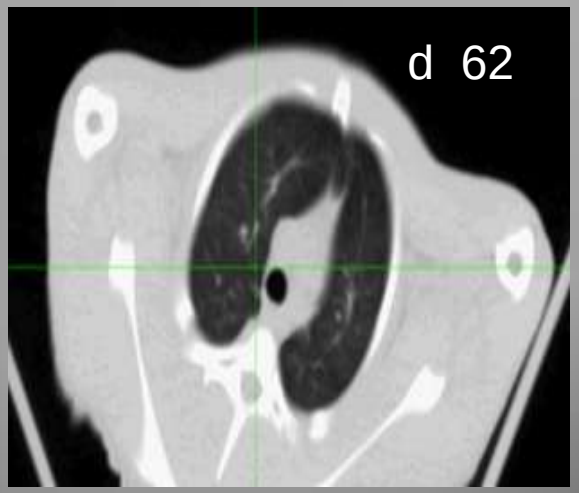


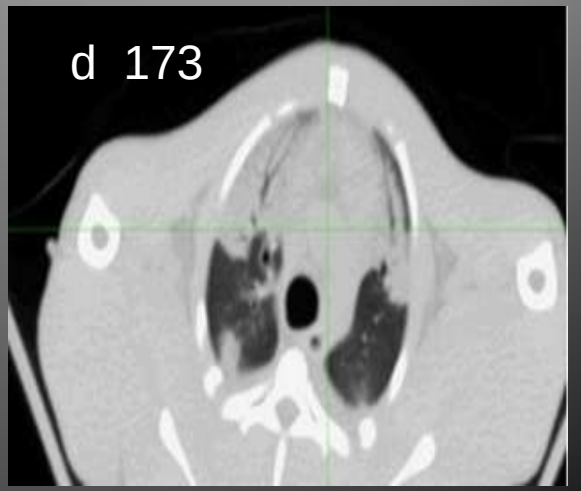


NHP 030489 10Gy
5%BM Shield



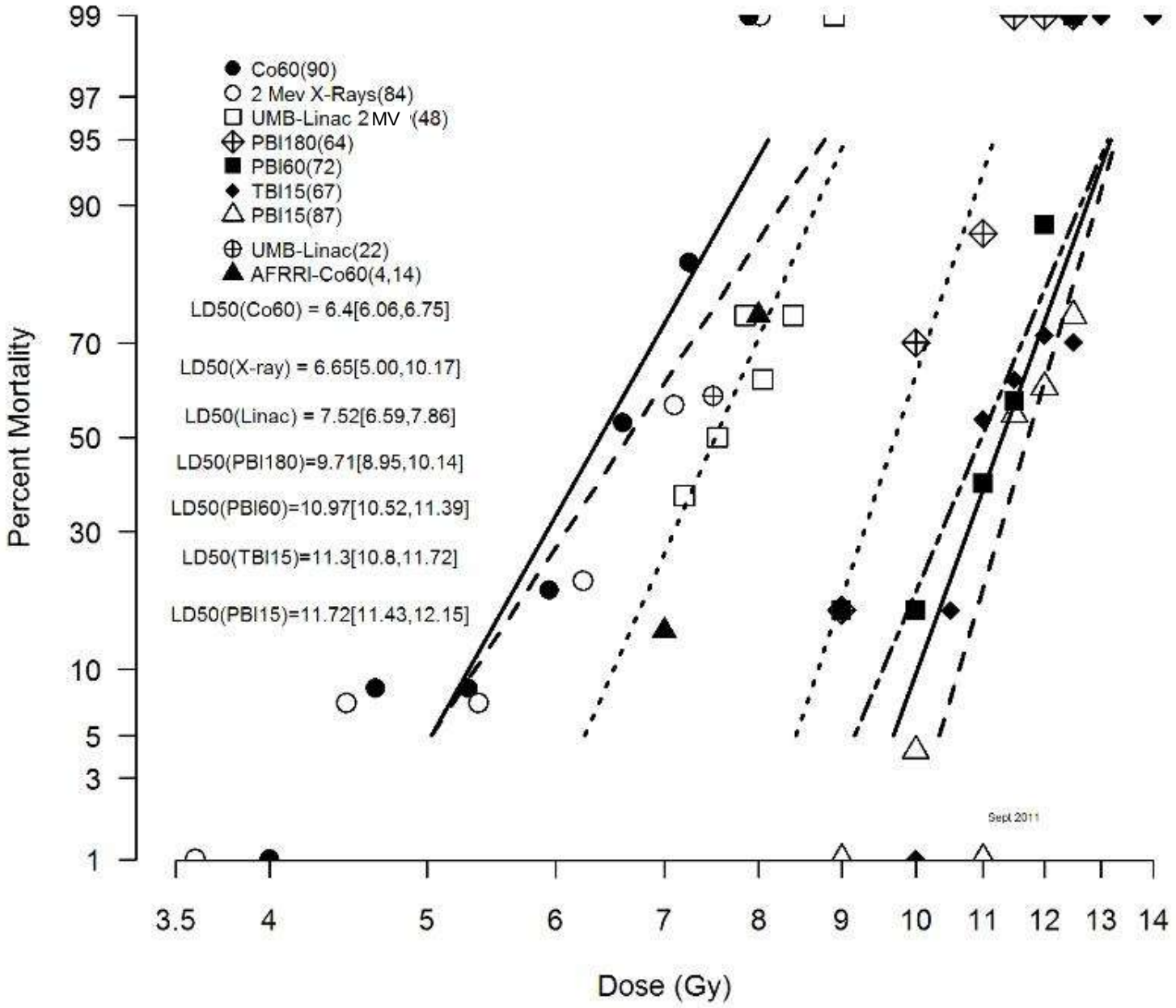
NHP 030609 11Gy
5%BM Shield





Radiation Dosimetry and Biology

- Rhesus macaque: LD50 estimates [95% C.I.]
  - TBI: H-ARS LD50/60, 7.52Gy [6.59, 7.86]
  - TBI: GI-ARS LD50/15, 11.30Gy [10.8, 11.72]
  - PBI/BM5: LD50/15, 11.73Gy [11.43, 12.15]
  - PBI/BM5: LD50/60, 10.97Gy [10.52, 11.39]
  - PBI/BM5: LD50/180, 9.71Gy [8.96, 10.14]
  - WTLI: whole thorax lung irradiation, TBD ongoing study


Rhesus macaques: TBI : H-, GI-ARS, and PBI/BM5
GI, H+GI, H+GI+lung DEARE
Co60(90)
2 Mev X-Rays(84)
UMB-Linac 2MV (48)
PBI180(64)
PBI60(72)
TBI15(67)
PBI15(87)
UMB-Linac(22)
AFRRI-Co60(4,14)
LD50(Co60) = 6.4[6.06,6.75]
LD50(X-ray) = 6.65[5.00,10.17]
LD50(Linac) = 7.52[6.59,7.86]
LD50(PBI180)=9.71[8.95,10.14]
LD50(PBI60)=10.97[10.52,11.39]
LD50(TBI15)=11.3[10.8,11.72]
LD50(PBI15)=11.72[11.43,12.15]
Sept 2011
Percent Mortality
99
97
95
90
70
50
30
10
5
3
1
3.5
4
5
6
7
8
9
10
11
12
13
14
Dose (Gy)

Radiation Dosimetry and Biology

- Rhesus macaque: Dose response for organ-specific lethality.
  - **TBI: H-ARS**, LD10 to LD90/60; 6.51Gy – 8.70Gy = **2.19Gy range**
  - **TBI**: **GI-ARS**, LD10 to LD90/15; 10.02Gy – 12.74Gy = **2.72Gy range**
  - **PBI/BM5: GI-ARS** LD10 to LD90; 10.02 – 12.74Gy = **2.72Gy**
  - **PBI/BM5: GI-, H-ARS + GI pro-ARS**, LD10 to LD90/60; 9.54Gy – 12.62Gy = **3.08Gy range**
  - **PBI/BM5: GI-, H-, GIpro-ARS, + lung-DEARE**, LD10 to LD90/180; 8.71Gy – 10.83Gy = **2.12G range**
  - LD10 to LD90 range is 2.12Gy to 3.08Gy

Radiation Dosimetry and Biology

- Rhesus macaque: Dose response for organ-specific lethality.
  - 10% Variability in Dose
  - PBI BM5
  - LD50/15 : Acute GI = 11.7 Gy
  - 5% > (0.60 Gy) = 12.3 Gy = LD75/15
  - 5% < (0.60 Gy) = 11.1 Gy = LD25/15

Radiation Dosimetry and Biology

- Rhesus macaque: LD50 estimates [95% C.I.]
- Respective “dose response” permits estimates for LD30, 50 and 70 for design of MCM efficacy and pivotal trial studies.
  - Recent study: Determine efficacy of neupogen (G-CSF) to enhance survival of lethally irradiated NHP.
  - TBI: H-ARS LD50/60, 7.52Gy [6.59, 7.86]
  - Study parameters: TBI at 7.50Gy +spt care
  - Est. LD50/60; G-CSF admin at 24h, then qd thru effect (ANC > 1,000/ul)
  - Stats designed for 30% inc in Survival to show efficacy.
  - Results:
  - control LD 59.1%, n=22 vs neupogen LD20.8%, n=24
  - P = 0.004

Radiation Dosimetry and Biology
The LD90:LD10 value

- Rhesus macaque: Dose response for mortality due to organ-specific and multi-organ injury.
  - TBI: H-ARS, 1.34 *H-ARS, 1.45; ** H-ARS, 1.55
  - TBI: GI-ARS, 1.27
  - PBI/BM5: GI-ARS, 1.22
  - PBI/BM5: GI-, H-ARS + GI pro-ARS, 1.32
  - PBI/BM5: GI-, H-, GIpro-ARS, + lung-DEARE, 1.24

*, ** historical data bases, 1967, Eltringham; 1965, Dalrymple

Radiation Dosimetry and Biology

- Human and canine: Dose response for mortality due to organ-specific and multi-organ injury.
  - The LD50/60 and LD90:LD10 value
  - **Canine:** TBI: H-ARS,
  - LD50/60 = 3.38Gy [3.23, 3.50], (+) spt care
  - LD50/60 = 2.58Gy [2.48, 2.68], (-) spt care
  - LD90:LD10 = 1.29 **(+) spt care**
  - **Human:** TBI, relative homogeneous H-ARS, GI-ARS
  - LD50/60 = 4.5Gy (MLT)*
  - LD90:LD10 = 2.26
  - LD50/7-14 = 9.6Gy** (MLT)
  - LD90:LD10 = 3.01
  - * Anno G et al Health Phys 84:565, 03; ** NRC study (NUREG/CR-6545, 1997)

Radiation Dosimetry and Biology

- Acknowledgements:
  - Radiation Physics: K. Prado, G. Lasio, W. Lu
  - Preclinical Radiobiology Lab: 15 staff; Statistics Core
  - NIAID: D. Cassatt, B. Maidment, E. Davies