RLIP76 Protein Reduces 4-HNE Generated During Oxidative Stress and Results in Protection in Well Characterized Animal Models of Acute Radiation Syndrome

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FDA Animal Rule

The Animal Rule states that FDA will rely on evidence from animal studies to provide substantial evidence of effectiveness only when all of the following four criteria, paraphrased below, are met (blue font=example for this program):

1. Reasonably well-understood pathophysiology of *hematopoietic-acute radiation syndrome (H-ARS)* and its prevention or substantial reduction by *RLIP76*
2. The effect is demonstrated in a *mouse model* expected to react with a response predictive for humans
3. The animal model endpoint is clearly related to the desired benefit in humans, *…survival…*
4. The data on the kinetics and pharmacodynamics of *RLIP76* allows selection of an effective dose in humans

If all of these criteria are met, it is reasonable to expect the efficacy of the drug in animals to be a reliable indicator of its effectiveness in humans.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf

Translational Medicine

- The “trick” is properly characterizing the animal models to bridge nonclinical and predicted clinical outcome

  - Shared proof-of-concept studies to avoid duplication (ex. - NIAID sponsored)
  - FDA surveys of existing successes to standardize endpoints (ex. – antidepressant investigation in Adv. Reg. Sci. for Public Health, Oct ‘10)
  - Sponsors use of ‘FDA Accepted’ surrogate markers, correlates of protection, clinical observations in animals, pathology, etc. (FDA Drug Development Tools)

National Institute of Allergy and Infectious Diseases

Medical Countermeasures Against Radiological Threats (MCART) Consortium

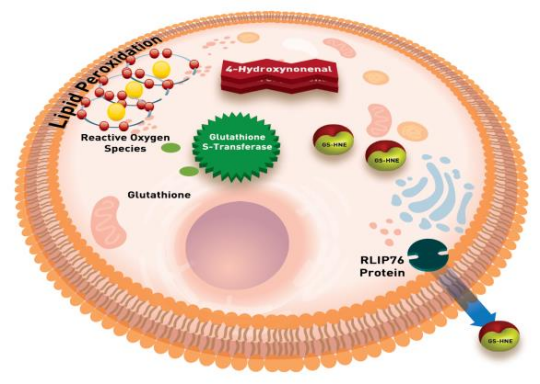
- Composed of 15 different research, development, regulatory, and administrative entities from the United States, Canada, and England
- Evaluates the potential efficacy of drugs and biologics that can be used to treat acute radiation syndrome(s)
- Characterized AND PUBLISHED animal models to be used in drug development programs by government and private entities
- *Health Physics*; October 2012; 103(4)

Transition to Industry

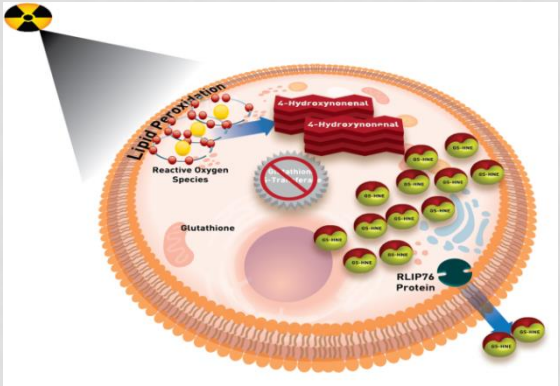
- Utilize the same experimental designs and demonstrate reproducibility across private laboratories
  - Identify a drug candidate with appropriate mechanism of action
  - Choose the appropriate species for efficacy testing
  - Establish the LD50 for H-ARS and secondary endpoints in untreated animals
  - Determine level of supplemental care (e.g., fluids,antibiotics,etc.)
  - Prove reproducibility of “natural history” studies
- Begin animal studies to advance the drug development program

Mechanism of Action

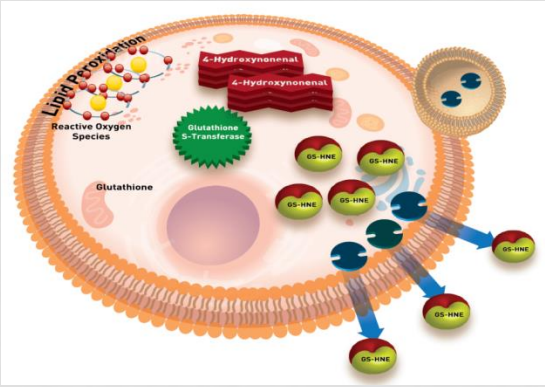
RLIP76 protein is part of the natural pathway to remove toxins of oxidative stress



External insults overwhelm the normal pathway; leading to cell damage / death



Additional RLIP76 protein allows natural mechanisms to protect or rescue the cell



Overview – "Company" Example

- Mouse model for H-ARS (C57BL/6 unless noted)
- 50% each sex; n=12/group; total body irradiation
- RLIP76-PL administered as 3 doses, in general
- Primary endpoint = survival at Study Day 30
- No supplemental or supportive treatment

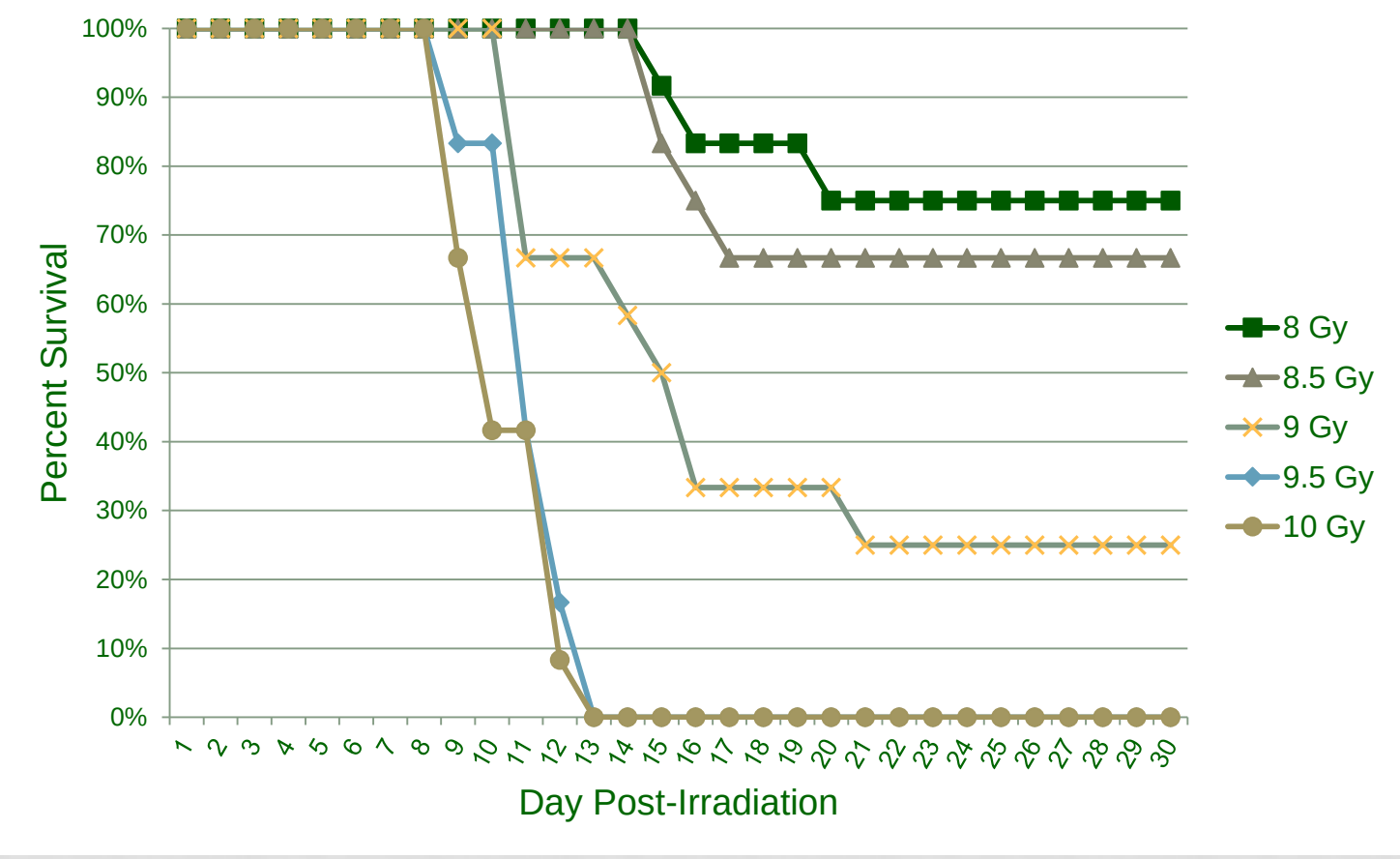
- Established LD50s for several radiation sources and several mouse strains
- Completed efficacy studies in multiple facilities
- Total body irradiation was used for doses from 7.45Gy to 8.75Gy

Results:

- Prophylactic dosing resulted in 100% survival (compared to 33% in controls)
- Therapeutic dosing (1st dose = 24hr post-exposure) resulted 92% survival (compared to 8% in controls)

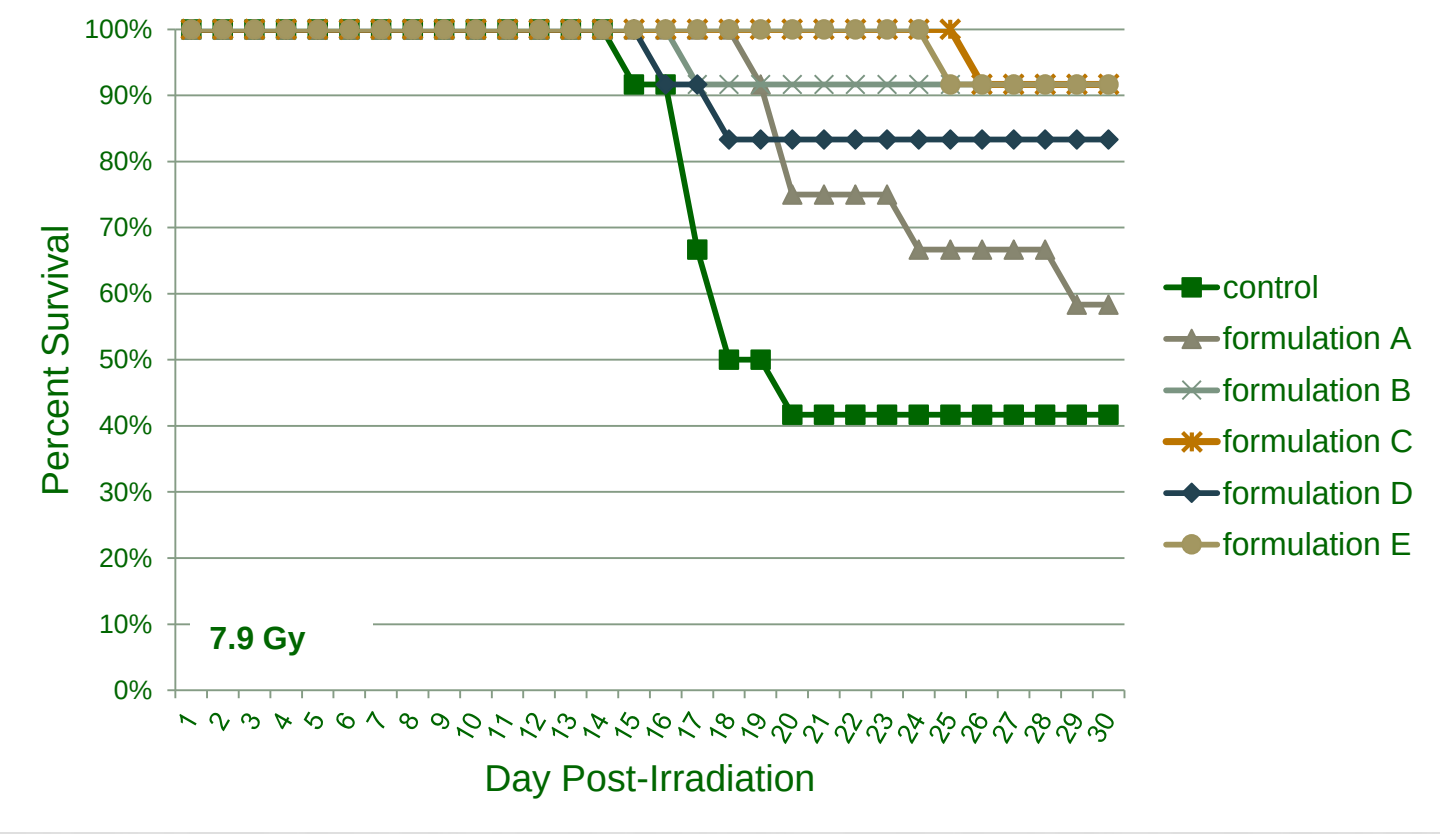
Establish the LD50

30-day survival studies were completed to determine lethal doses after total body irradiation



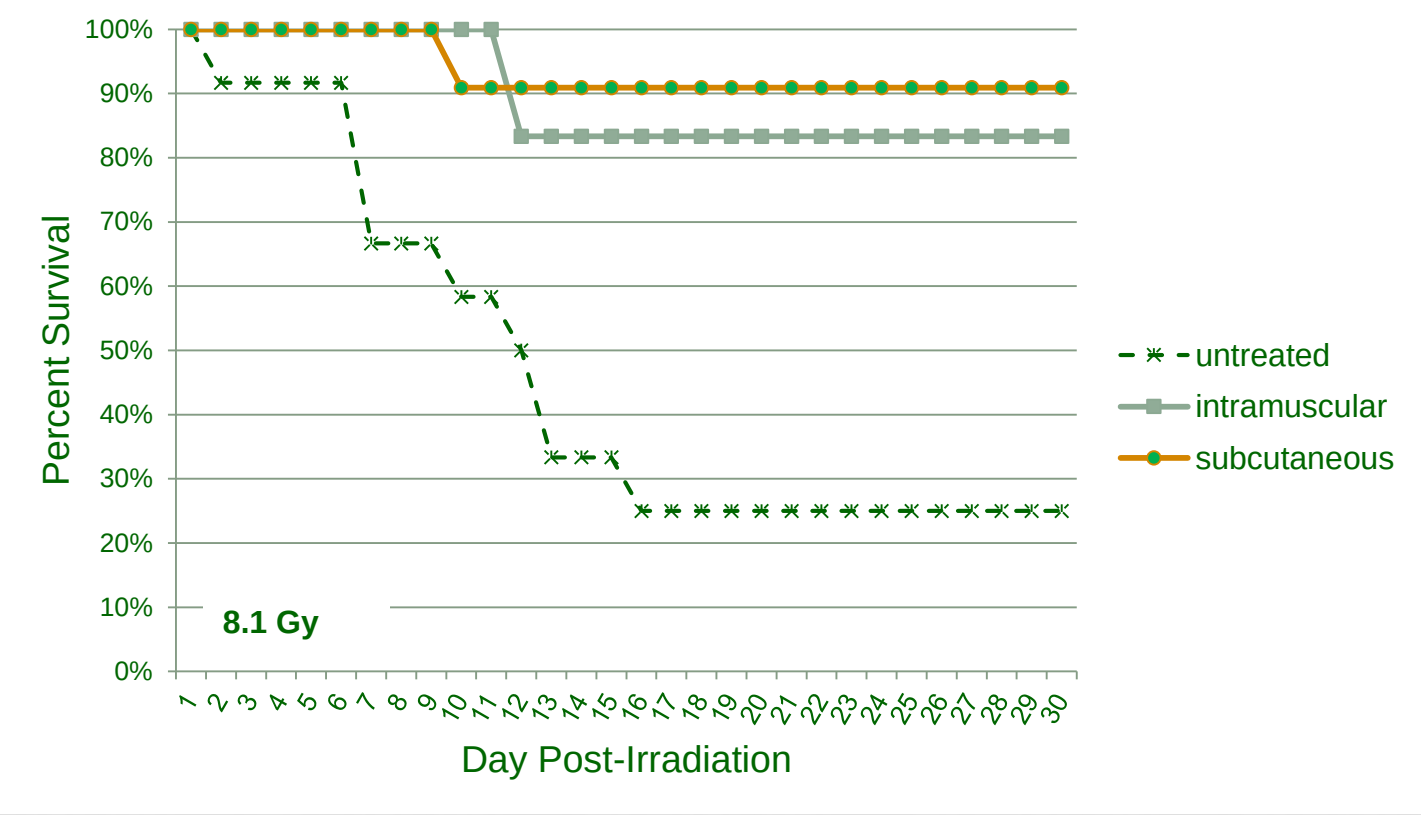
Down-select Formulations

- Prophylactic subcutaneous administration: -20hr, -3hr, +3hr
- Formulations C and E were superior, but Formulations B and D passed



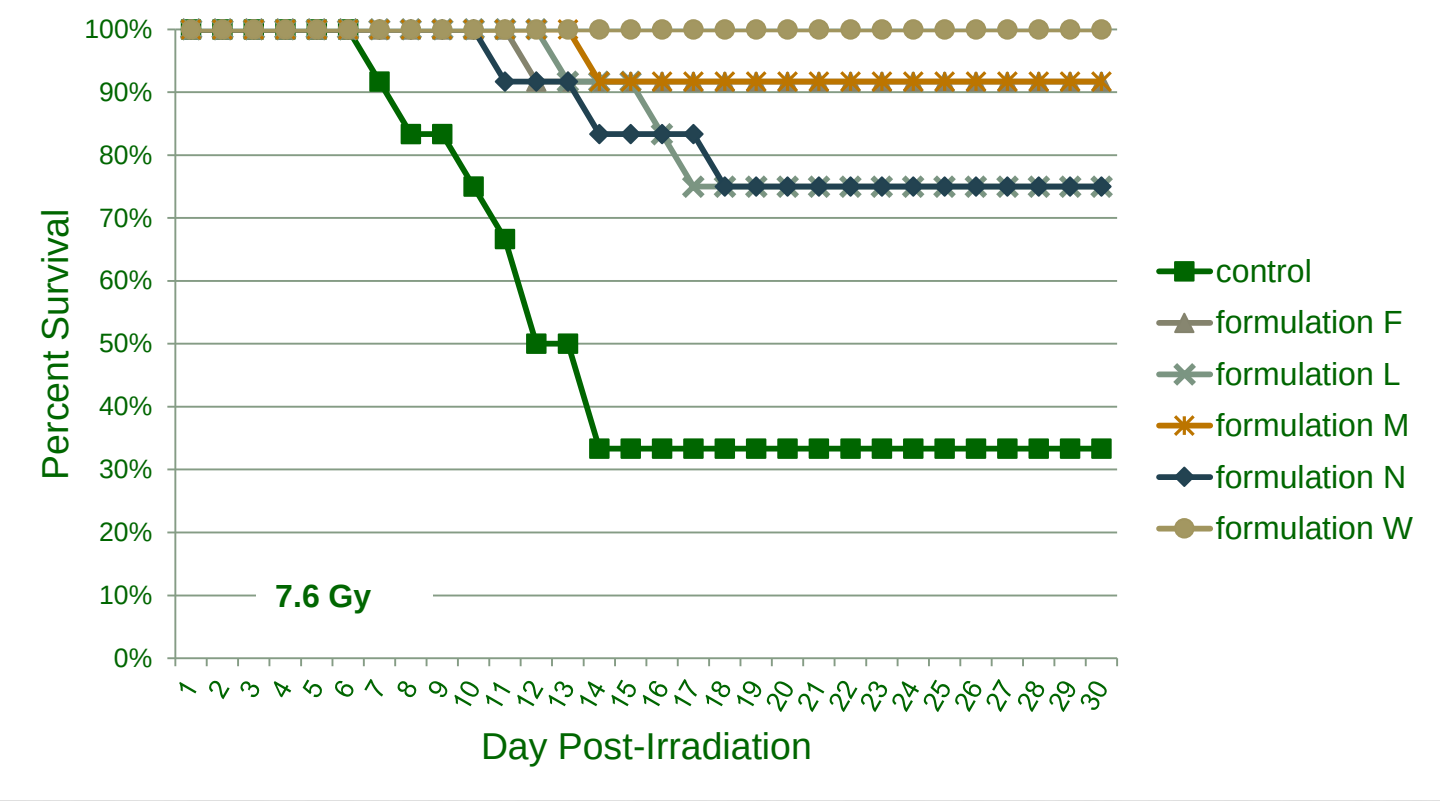
Route of Administration

- Therapeutic administration: +4hr, +12hr, +24hr
- Either route resulted in excellent rates of survival – subcutaneous was selected based on USG requirements



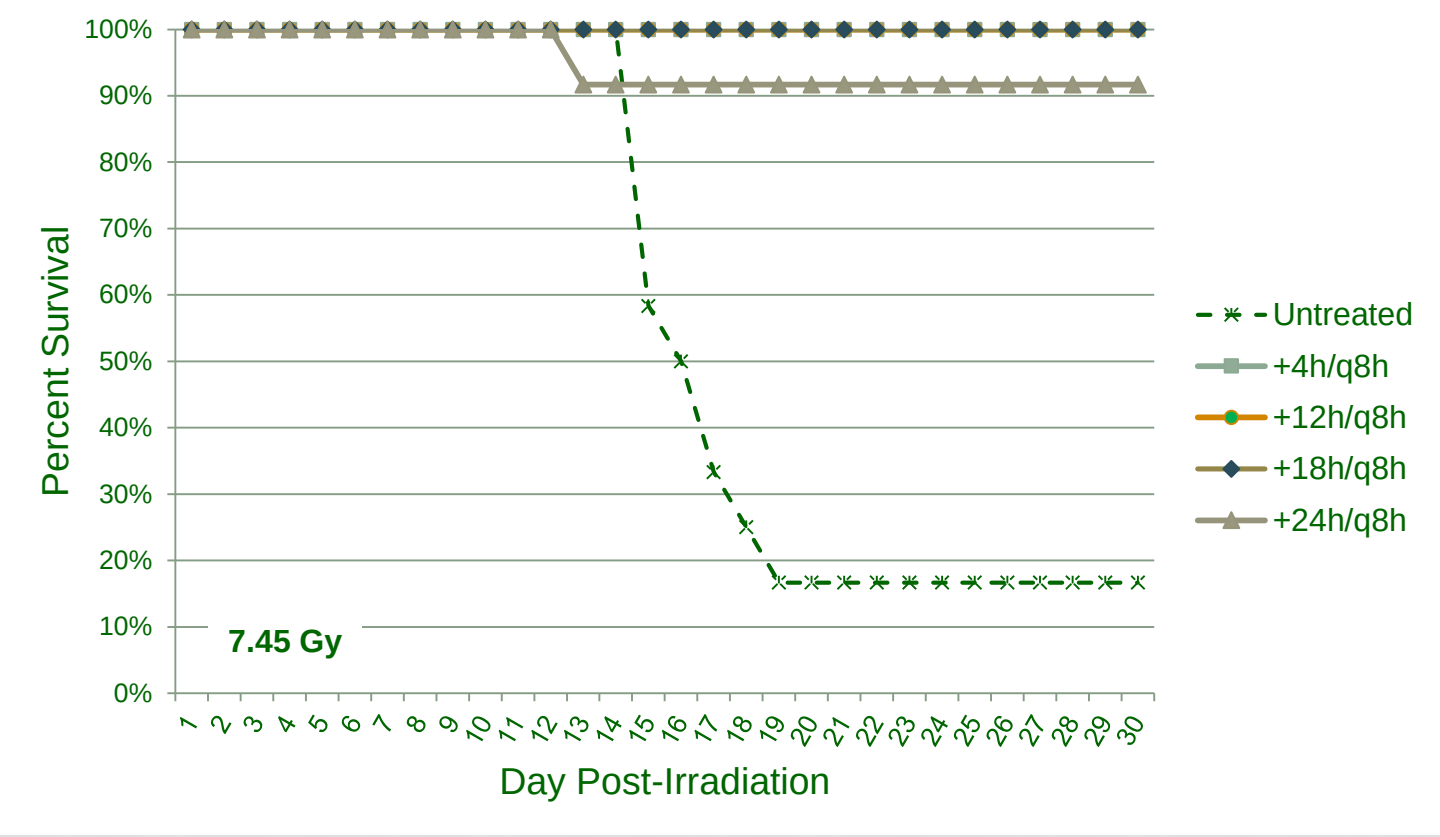
Post-Exposure Therapeutic Proof-of-Concept: Early Administration

- Therapeutic administration: +4hr, +12hr, +24hr
- Success of a formulation administered early was used to determine what formulation to advance to a 'delayed administration trial'



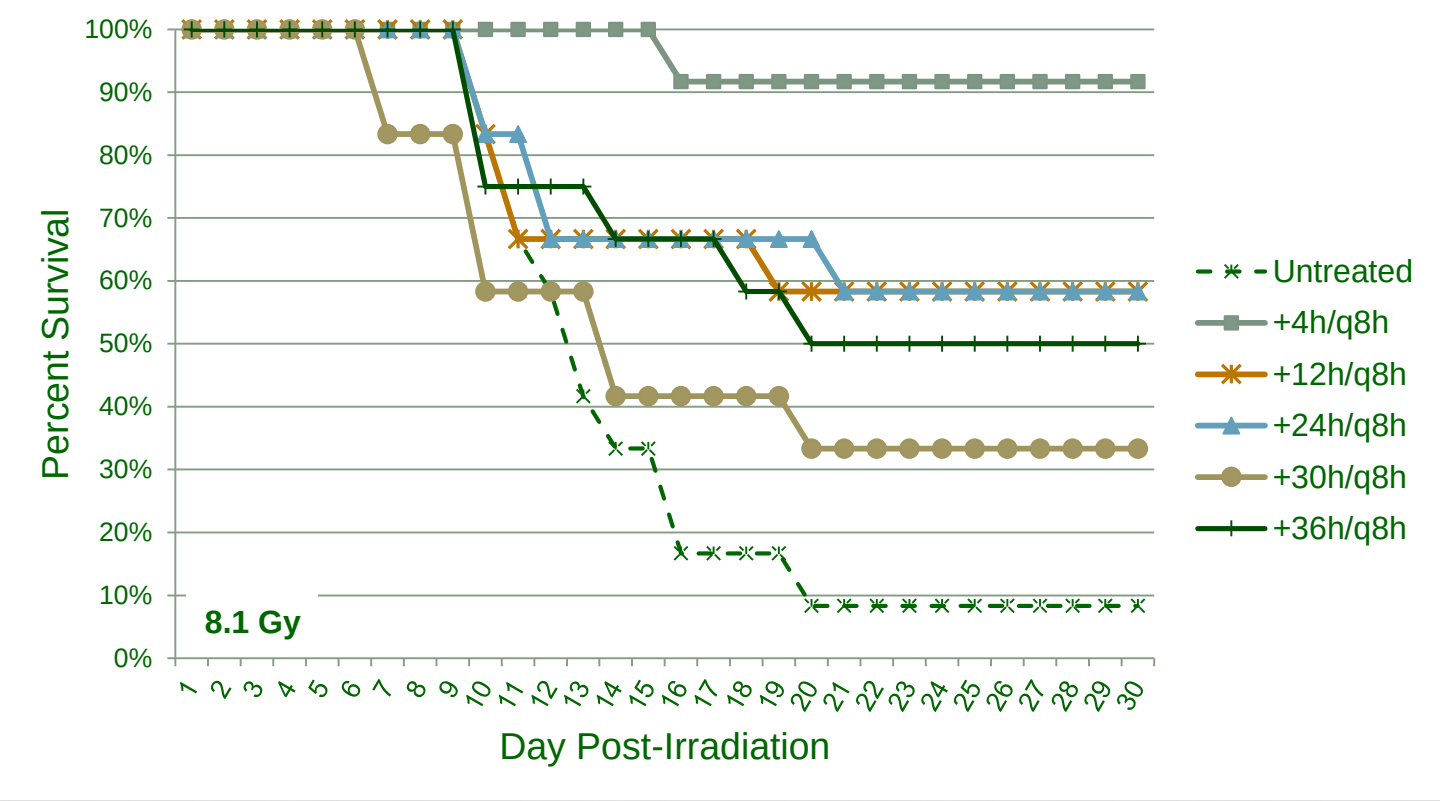
Post-Exposure Therapeutic Delayed Administration

- 1st of 3 doses were administered at time shown (C3H mice)
- Delaying an entire day still provided an increase of 84% survival



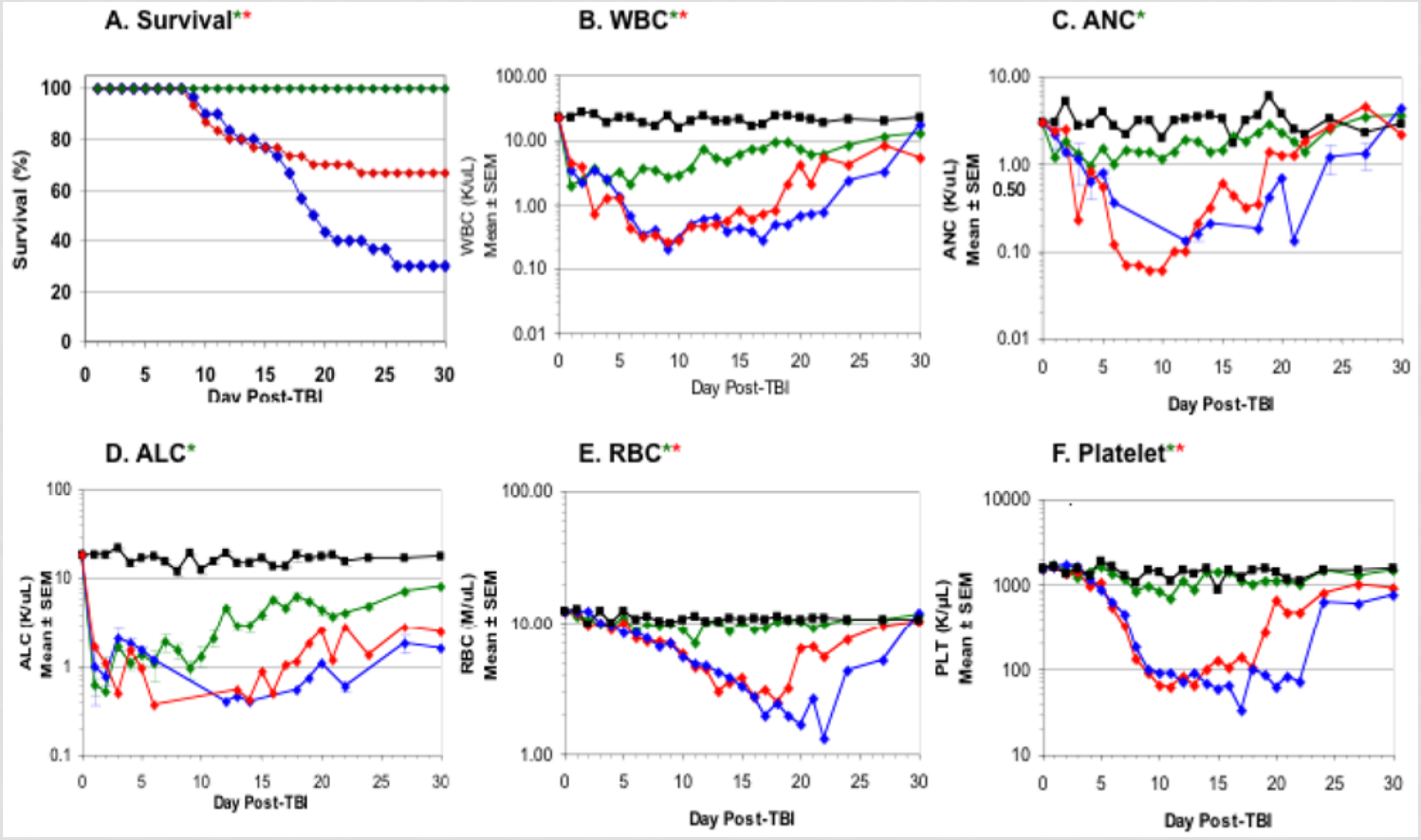
Post-Exposure Therapeutic Extending the Time to First Dose

- 1st of 3 doses were administered at time shown
- Delaying 30-36hrs still provided protection in up to 50% of the mice



Next Steps: 2º Endpoints

Examples – from MCART team



Plett PA, et al. Establishing a murine model of the hematopoietic syndrome of the acute radiation syndrome. Health Phys. 2012 Oct;103(4):343-55.

Conclusions

- NIAID sponsored a strong team (MCART) to characterize the animal models for acute radiation syndromes
  - Primary endpoint of survival
  - Secondary endpoints have also been described, depending on the syndrome
- The models have been used to seek licensure (e.g., Neupogen®) using the FDA Animal Rule
- Biopharmaceutical companies will be able to transition these models and employ them in advanced drug development – strengthening the translational bridge between nonclinical efficacy and human protection

Questions

Thank you for your attention!

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