



Radiation Countermeasures Symposium: Introduction

AFRRI 50th Anniversary

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Background



- 1945: Hiroshima & Nagasaki, “Radiation Sickness” spurred research on radiation injury, radiation countermeasures, hematology
- 1949-1950s: Thiols (SH-containing molecules) protected animals from acute radiation syndrome (ARS). Free radical scavengers
- 1950s-1980s: US Army (WRAIR) advanced phosphorylated aminothiols. Prototype: WR-2721 (amifostine, Ethiol®)

Background, cont.



- 1950s: Microbial constituents, immunomodulators (e.g., endotoxin, John Ainsworth, future SD of AFRRI)
- 1950s: Radiation-induced septicemias in mice partially controlled with antibiotics

AFRRI's Past



- 1960 (groundbreaking): AFRRI established as joint military research institute, focus on “high-dose external radiation effects on biological systems” and “casualty criteria.”
- 1976: AFRRI’s mission broadened to include “diagnosis and therapy of radiation injury”
- 1980s: AFRRI investigated relationship between efficacy and toxicity of WR aminothiols (PIs: Joseph Weiss, Victor Bogo, Michael Landauer). Toxicity prevents use in field

AFRRI's Past, cont.



- 1980s-1990s: AFRRI explored proper management of radiation-induced sepsis based on studies of GI flora and antimicrobials (PIs: Thomas Elliott, David Ledney, Itzhak Brook)
- 1980s-1990s: AFRRI studied use of immunomodulators: microbial constituents and analogs (PIs: Myra Patchen, Thomas MacVittie, David Ledney, Thomas Elliott, Itzhak Brook)
- 1986: Realizing immunomodulator actions mediated by cytokines, AFRRI introduced cytokines as radiation countermeasures in mice (PI: Ruth Neta)

AFRRI's Past, cont.



- Late 1980s-1990s: AFRRI followed up with cytokines in large animal models (PI: Thomas MacVittie).
- AFRRI's work led to current use of cytokines, e.g., G-CSF, as standard treatment for radiation casualties
- CDC currently holds IND and Emergency Use Authorization applications for G-CSF (Neupogen[®]) in case of radiation incident
- Neupogen[®] in Strategic National Stockpile

AFRRI's Present



- Mission: research leading to products that will preserve the health and performance of U.S. military personnel and civilians exposed to ionizing radiation
- Mission is primary goal: grants, publications essential for obtaining funds to perform mission-oriented research

AFRRI's Present, cont.



- Integrating basic and applied research
- 75% of research funds come from competitive extramural sources (NIH, NASA, DTRA, DMRDP, CDMRP, etc)
- Focus on radiation countermeasure candidates with realistic chance of success (route, toxicity, etc)
- High throughput radiation sources (photons, neutrons)
- Coordination between industry, academia, regulatory agencies

AFRRI's Present, cont.



- Five countermeasures for ARS have FDA Investigational New Drug (IND) or Emergency Use IND status (G-CSF). Four were conceived at AFRRI, and one was initiated elsewhere, with AFRRI recruited for collaboration at an early stage.
 - 5-Androstenediol (5-AED): Conceived, initiated, developed by AFRRI. AFRRI recruited private company for advanced development. Prototype non-toxic small molecule countermeasure (PI: Mark Whitnall) IND: 2005 (1st IND for an ARS countermeasure)
 - BIO 300 (genistein): Conceived, patented, initiated, developed by AFRRI. AFRRI recruited private company to aid advanced development. Small molecule anti-apoptotic kinase inhibitor (PI: Michael Landauer) IND: 2007

AFRRI's Present, cont.



- Radiation countermeasures with FDA IND status, cont.
 - Ex-Rad[®]: Conceived at AFRRI, private company obtained funding, collaborated with AFRRI for R&D. Small molecule anti-apoptotic kinase inhibitor (PIs: originally Sree Kumar, now Sanchita Ghosh) IND: 2008
 - CBLB502: Private company recruited AFRRI to aid R&D at early stage. Truncated flagellin immunomodulator (PIs: originally Mark Whitnall & V Srinivasan, now Vijay Singh) IND: 2008

AFRRI's Future

- **Intramural Screening Program (internally funded)**
 - PI: Sanchita Ghosh
- **Countermeasure efficacies against neutron/gamma (high LET)**
 - Barbara Ngudiankama, Lynn Cary & Mark Whitnall, extending previous work of David Ledney
- **Animal Model Development: Minipig for ARS**
 - Maria Moroni & Mark Whitnall

AFRRI's Future



- **Combined Injury/GI/Systemic Interactions**
 - PIs: Juliann Kiang, David Ledney, Thomas Elliott, extending previous work of David Ledney
- **Late Effects**
 - PI: Alexandra Miller

AFRRI's Future, cont.



- **Continue Basic Program**

- Required for Animal Rule
- Target Discovery
- 'Omics, Bioinformatics
- Discussing High Throughput Screening, Rational Drug Design, etc (how productive?)

- **Funding for Advanced Drug Development**

- DoD: Transition of AFRRI products with Chemical Biological Medical Systems (CBMS)
- HHS: BARDA (GLP, etc)

Policy Questions



1. Pre vs. Post

- a. Pre: Emergency Responders, Emergence from Sheltering-in-Place, Military Personnel
- b. Post: Civilians and Military Personnel

Should radiation countermeasure development for civilian use include pre-irradiation measures?

Policy Questions

2. 24 h Delay before drug administration

- a. Assumes medical treatment facilities available after evacuation from mass disaster area within 24 h. (How likely?)
- b. Animal studies: is 24 h of ARS in animals the same as 24 h of ARS in humans?
- c. Most mitigators work better given early after irradiation.

Should radiation countermeasure development for civilian use include agents to be given within hours after irradiation?

Policy Questions



3. Far-forward fielding

- a. Storage of countermeasures in hospitals, police stations, etc.
- b. Rapid deployment of agents under control of local authorities
- c. HHS CHEMPACK in use for nerve agent countermeasures
- d. Would allow administration of drugs within hours
- e. Discussed for countermeasures to internalized radionuclides (RADPACK): Western J Emergency Med 9 (2008):
<http://escholarship.org/uc/item/7rt8b6mr>

Far-forward fielding of countermeasures to ARS?

Policy Questions



4. Administration route

- a. Oral easiest?
- b. Subcutaneous relatively easy
- c. If nausea and vomiting – oral not recommended
- d. Protective gear including headgear in contaminated environment – not recommended to remove headgear to take a pill
- e. Intramuscular in use for military self-admin or buddy admin
- f. Intravenous if medical personnel available (how likely?)

Which administration routes are priorities?

Policy Questions



5. Small molecule vs large molecule

- a. Large molecules may require iv administration: how practical if medical personnel unavailable?
- b. Large molecules may be less stable: require refrigeration or freezing, issues for storage and transportation

Should the focus be on small molecules?

Policy Questions



6. Cellular therapy, gene therapy

- a. IV admin if medical personnel available (how likely?)
- b. Medical expertise requirements?
- c. Possible adverse consequences?

What is the role of cellular therapy and/or gene therapy in response plans?

Policy Questions



7. Mass casualty vs small-scale scenario
 - a. Whether there is prompt evacuation and medical support affects administration route, early administration, medical expertise available
 - b. What are the triggers for transportation paralysis and communication overload that would affect evacuation and medical response plans?

For which scenarios are we planning and funding?

Should availability of clinical support be assumed?

Policy Questions



8. GI Syndrome: FDA issues

- a. Traditional GI syndrome: death within 6-14 days due to GI injury (fluid and electrolyte imbalance, bacterial translocation)
- b. Traditional countermeasure success: survival beyond that period, with evidence of lessening of GI injury
- c. FDA criterion of success for any radiation countermeasure under Animal Rule: long-term survival? (Need to cure hematopoietic syndrome when assessing GI countermeasures?)

How does GI syndrome fit into approval of radiation countermeasures?

Policy Questions

9. GI Syndrome: definition issues

- a. Length of survival monitoring period for “GI syndrome” has been creeping up in mice and monkeys
- b. Now ending just before main mortality period of “hematopoietic syndrome”
- c. Starting to seem somewhat arbitrary: early deaths can occur from hematopoietic syndrome
- d. Support statements about cause of death with GI histopathology (Rotolo, Kolesnick, Fuks. Int J Rad Oncol Biol Phys 73: 6-8, 2009)
- e. Multi-organ dysfunction/failure vs ARS sub-syndromes

Current status of ARS sub-syndrome concept?

Policy Questions

10. Funding

- a. Big Pharma generally not interested in countermeasures to weapons of mass destruction – not their business model
- b. Small companies get to IND, then need funds for large scale efficacy (Animal Rule) and multi-center human safety trials
- c. Funding for Rad-Nuc small compared to Chem and Bio

Government's role in funding advanced radiation countermeasure development?

Relative funding for Chem, Bio, Rad-Nuc?