

Evaluation and Development of Radiation Countermeasures at AFRRRI

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ABSTRACT

Leukopenia after ionizing radiation is due largely to free radical injury to stem cells and progenitors in hematopoietic tissue. Recovery depends on the ability of the remaining stem cells and progenitors to proliferate and differentiate sufficiently to reconstitute the immune system before a lethal infection takes hold. Proliferation and differentiation of hematopoietic progenitor cells (HPC) are dependent on factors produced by cells in the hematopoietic microenvironment or niche. We recently introduced a novel class of radiation countermeasures, the 5-androstene steroids. The prototype compound is 5-androstenediol (5-AED), a natural steroid that enhances survival in irradiated animals. We demonstrated that 5-AED stimulates hematopoiesis, ameliorates neutropenia, activates immune cells, and induces cytokine expression. Pilot studies in non-human primates have shown positive results and have led us to enter a phase of advanced drug development with this compound. To develop 5-AED for use in humans, it is necessary to better understand the mechanisms by which 5-AED produces these effects. A detailed mechanistic understanding is important because the pivotal efficacy studies involving whole-body irradiation will be performed in non-human primates, under the U.S. Food and Drug Administration's "Animal Efficacy Rule." A thorough analysis of mechanisms of action of 5-AED is required by the FDA in order to predict efficacy in humans. Knowledge of 5-AED's mechanisms of efficacy also will be helpful in guiding the discovery and evaluation of other classes of radiation countermeasure candidates. We are investigating induction of cytokine expression and modulation of apoptotic signaling pathways by 5-AED in blood-forming tissue, on the mRNA and protein levels. We are also exploring the effects of 5-AED on the various cell lineages of the immune system, and testing the possible role of specific niche cells in 5-AED's stimulation of hematopoiesis. A similar process of baseline assessment, detailed evaluation, and advanced drug development is being undertaken at AFRRRI for a portfolio of promising countermeasure candidates. Our criteria for admitting drug candidates into this program are evidence for radioprotectant, immunostimulatory, or cancer-preventative activity, representation of different mechanisms in the program, low toxicity, a practical administration route, and pre-existing human safety data. Compounds being evaluated at AFRRRI include soy isoflavones, vitamin E-related compounds, phenylacetate, phenylbutyrate, epigallocatechin gallate (EGCG), benzyl styryl sulfones, CpG oligonucleotides, a superoxide dismutase mimetic, statins, dipeptidyl peptidase inhibitors, and truncated flagellin.

1.0 INTRODUCTION

The risk of civilians and emergency responders being exposed to lethal doses of ionizing radiation is greater now than it was during the cold war. Nuclear proliferation, terrorist activity, and the distribution of nuclear

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and radioactive materials through underground networks make incidents involving radiation injuries increasingly likely. Scenarios involving radiological hazards include nuclear detonations, covert placement of radioactive substances, and dirty bombs [Waselenko 2004]. At doses above about 1 Gray (Gy; gamma or X-rays) in humans, hematopoietic function is compromised, leading to decreases in white blood cell counts and increased susceptibility to infection [Armed Forces Radiobiology Research Institute 2003]. At doses above 2 Gy, some mortality is likely [Armed Forces Radiobiology Research Institute 2003]. The dose at which one half of exposed individuals would die (LD50) without medical support is estimated to be about 3.25 Gy in humans [Armed Forces Radiobiology Research Institute 2003]. Doses of 1 to 8 Gy and higher are likely to be experienced by dozens to thousands of people during the scenarios mentioned above [Waselenko 2004]. At doses above about 8 Gy, injury to the gastrointestinal (GI) system becomes serious and contributes to mortality [Armed Forces Radiobiology Research Institute 2003]. The acute consequences of exposures between about 1 and 8 Gy are termed the “hematopoietic syndrome,” while the acute effects after doses of about 8 to 30 Gy are known as the “GI syndrome” [Armed Forces Radiobiology Research Institute 2003]. The doses of radiation necessary to cause mortality will be lower in the event of deliberate exposure of civilian populations to pathogenic microorganisms. Combined use of radiological and biological weapons will result in a synergistic effect that will produce much higher rates of mortality than with either type of agent alone [Elliott 2002].

In view of the increasing likelihood of radiation exposure and bioterrorism, the need for fieldable countermeasures has been recognized as a high priority by government agencies. Such drugs should be easy to administer, have long shelf-lives at environmental temperatures, protective durations of at least 24 h, and should display extremely low toxicity. Currently the treatment of choice, other than basic clinical support including antibiotics, is the off-label use of bone marrow growth factors. These factors have been approved by the FDA for use in chemotherapy patients to stimulate blood-forming tissue, but not yet for use as radiation countermeasures. They need to be administered under the supervision of a physician. One goal at AFRRI is to develop countermeasures that have a safety and ease of administration profile that would make them suitable for use without direct involvement of physicians. We recently introduced a novel class of radioprotectants, 5-androstene steroids, with these properties [Whitnall 2000, Whitnall 2001, Whitnall 2002b]. The prototype compound is androst-5-ene-3 β ,17 β -diol (5-androstenediol, 5-AED, also known as HE2100 or NEUMUNE™), a naturally circulating hormone and metabolite of the adrenal steroid dehydroepiandrosterone (DHEA) [Loria 1992b]. 5-Androstene steroids normalize cytokine patterns after severe injury [Araneo 1995], and enhance survival after lethal doses of various species of bacteria, viruses, and parasites [Ben-Nathan 1991, Ben-Nathan 1999, Carr 1998, Daigle 1998, Loria 1992b, Loria 1996, Loria 2002, Rasmussen 1992, Whitnall 2000].

Administration of 5-AED to mice [Whitnall 2000, Whitnall 2001] and non-human primates [Stickney 2003] results in amelioration of radiation-induced neutropenia. In mice, 5-AED stimulates hematopoiesis [Loria 2002, Whitnall 2000], activates neutrophils, monocytes, and natural killer cells [Whitnall 2001, Whitnall 2002a], and enhances survival after whole-body gamma-irradiation [Loria 2002, Whitnall 2000, Whitnall 2002b]. Survival was enhanced after radiation alone and after radiation plus inoculation with lethal doses of gram-negative bacteria (*Klebsiella pneumoniae*) [Whitnall 2000]. In order to develop this compound for use in humans, it is necessary to better understand the mechanisms by which 5-AED produces these effects. A detailed mechanistic understanding is important because of the fact that the pivotal efficacy studies for FDA approval involving whole-body irradiation will be performed in animals, not humans. The FDA will require a thorough analysis of mechanisms of action of 5-AED before approval is given for use in humans. Furthermore, knowledge of the mechanisms mediating radioprotectant efficacy will guide the development of novel radioprotectants in the future. Therefore, we are using *in vivo* and *in vitro* techniques to explore the roles of

specific hematopoietic niche lineages, immune cell types, cytokines and other regulatory factors, and intracellular signaling pathways in the beneficial effects of 5-AED.

The long-term goal of this research program is to use the mouse and non-human primate models to understand mechanisms of radiation injury and pharmacological countermeasure efficacy in order to develop countermeasures for real-world radiation disaster scenarios. The process we followed for the discovery and development of 5-AED as a radiation countermeasure is now being applied to a portfolio of countermeasure candidates.

2.0 SELECTION OF RADIATION COUNTERMEASURE CANDIDATES

The current size of the program at AFRRI does not permit “screening”: we are not testing a large number of molecules that have little evidence to support their potential as anti-radiation agents, in the hope that a small percentage of them will emerge as promising candidates. Compounds that enter our program have already been screened by others and have emerged as attractive candidates according to the criteria discussed below. Nevertheless, the list of strong candidates greatly exceeds our ability to fully evaluate them within a few years because of the variety of studies that must be performed.

AFRRI is reaching out to academic and government laboratories and private industry to collect candidates for radiation countermeasures to test. In order to maximize the use of AFRRI resources, candidates are selected for preliminary evaluation based on the following criteria:

2.1 Prior Evidence of Effects Appropriate for a Radiation Countermeasure

Compounds with pre-existing evidence of effects that would ameliorate radiation injury, or stimulate recovery, are considered for evaluation by AFRRI’s program. Such effects could be immunomodulatory, free radical-scavenging, mimicking of antioxidant enzymes, or modulation of signaling pathways.

2.2 Representation of Different Mechanisms

There is a preference for choosing compounds that would contribute to a diversity of possible countermeasure mechanisms being explored at AFRRI. It is felt that this will maximize chances for finding optimal approaches, and also will facilitate combining different countermeasures for possible synergy.

2.3 Low Toxicity

Given the experience with previous countermeasure candidates that caused significant increases in survival after exposure to whole-body ionizing radiation but proved too toxic for use in the field, AFRRI is concentrating on approaches that have extremely low toxicity. The goal is a safety profile that would make a compound suitable for administration to large numbers of people who may be at risk of exposure, or who possibly have been exposed, but for whom precise radiation dosimetry is lacking. For some candidates, pre-existing human safety data are available because a drug or dietary supplement has been approved previously for another indication, which accelerates our evaluation and development process.

2.4 Practical Administration Route

An important goal of AFRRI’s countermeasure program is to identify and develop compounds that can be administered to personnel outside the clinic, without interfering with the ability of warfighters or emergency

responders to perform their duties. Oral or buccal administration are attractive options in this regard, but in some cases, subcutaneous (sc) or intramuscular (im) injections are feasible. Personnel in mission-oriented protective posture (MOPP) gear would not remove protective headgear to swallow a pill, but could use an im autoinjector, injecting through the suit into the thigh.

2.5 Stability at Environmental Temperatures

Compounds that are stable at environmental temperatures would maximize transport and storage options.

3.0 PRIORITIZATION

3.1 General Types of Experiments Performed to Prioritize Candidates

Due to the large number of countermeasure candidates being evaluated, simple survival experiments in mice are done to eliminate compounds that will not accomplish our main goal: to decrease mortality. Figure 1 shows an example of such an experiment for 5-AED. We selected 5-AED for testing because of its known ability to increase resistance to infection [Loria 1992a], low toxicity, ease of administration as a steroid, and stability at environmental temperatures.

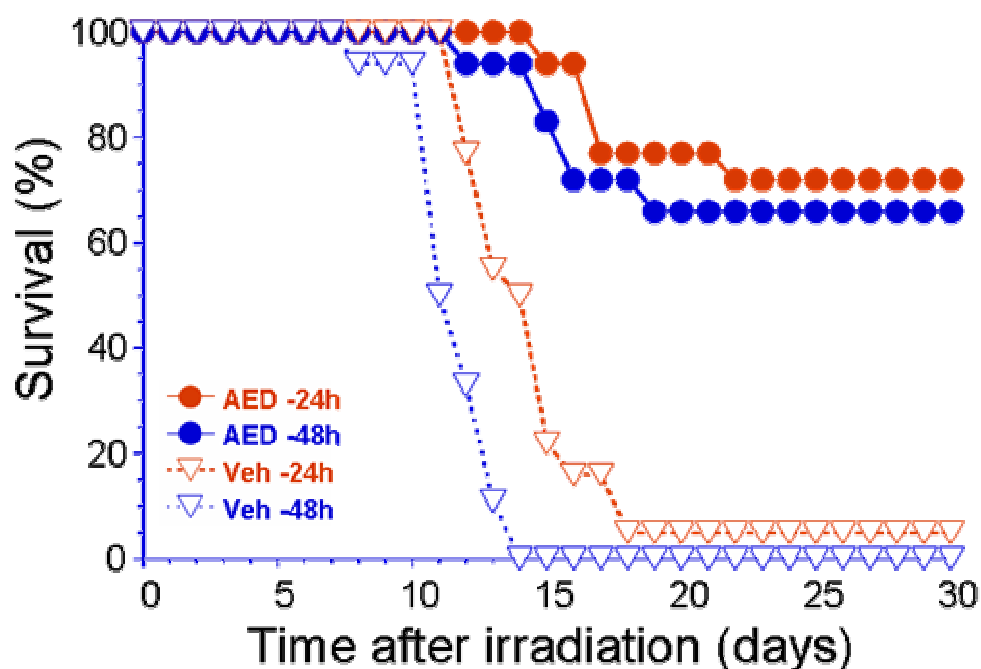


Figure 1: Survival in male C3H/HeN mice exposed to whole-body gamma radiation at a dose of 9 Gy. 5-AED in PEG-400 vehicle was injected sc 24 or 48 h before irradiation. Survival in each 5-AED-treated group was significantly greater than control ($p < 0.001$). From data presented in [Whitnall 2005].

4.0 BASELINE ASSESSMENT

Depending on the results of the prioritization phase, compounds are advanced to the level of baseline assess-

ment in mice. In this phase, dose reduction factor (DRF) studies are performed, and variations in route and timing of administration are tested. The data provide an initial assessment of the potential of a candidate, and indicate possible flexibility in terms of administration parameters. However, exhaustive permutations of administration parameters are not explored in mice because of possible differences in pharmacokinetics between rodents and primates. DRF studies are the best way to compare efficacy between compounds because a range of radiation doses is used. Evaluations based on a small range of radiation doses can be difficult to interpret because of the steepness of the survival-radiation dose curve. DRFs are based on the shift in probit lines in groups of animals given different treatments. The DRF is the ratio between the LD50 of the treated group to the LD50 of a control group. Figure 2 shows an example of a DRF study for 5-AED.

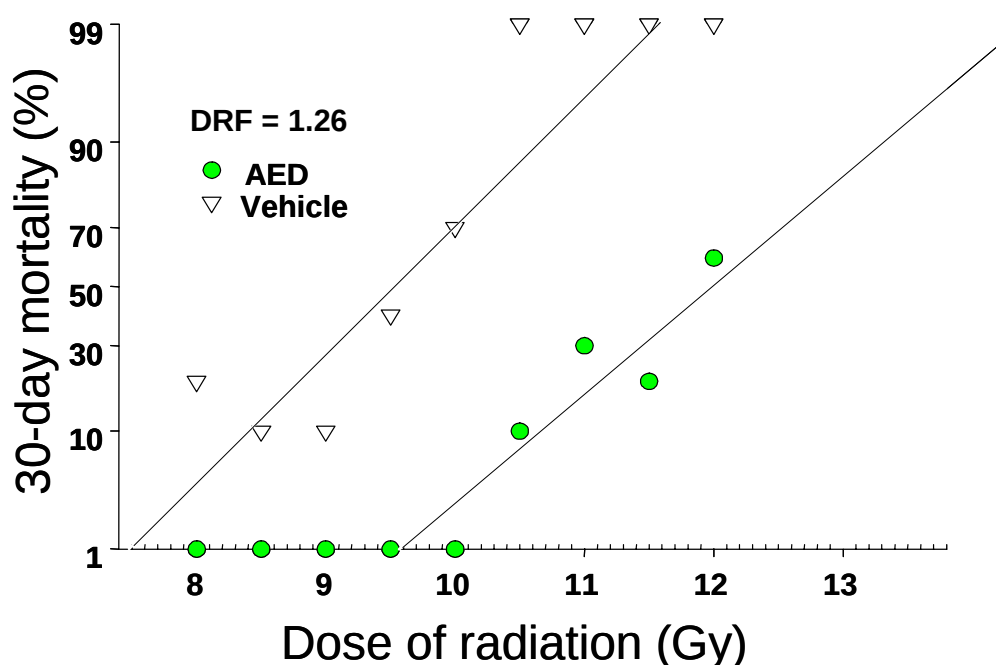


Figure 2: Survival in female B6D2F1 mice exposed to whole-body gamma radiation. 5-AED in PEG-400 vehicle was injected sc 24 h before irradiation. The probit line was shifted to the right in the 5-AED-treated group ($p < 0.001$). The 95% confidence limits of the DRF were 1.20 - 1.35. From data presented in [Whitnall 2000].

The oral route usually is tested because of its great advantage in terms of practicality in the field. 5-AED demonstrated some efficacy with oral gavage (Figure 3) but further development is needed to make this feasible.

5.0 DETAILED EVALUATION

If a compound appears promising after baseline assessment, preliminary experiments are performed in mice to explore mechanisms of action and toxicity. Because a key goal of most countermeasures is to ameliorate the

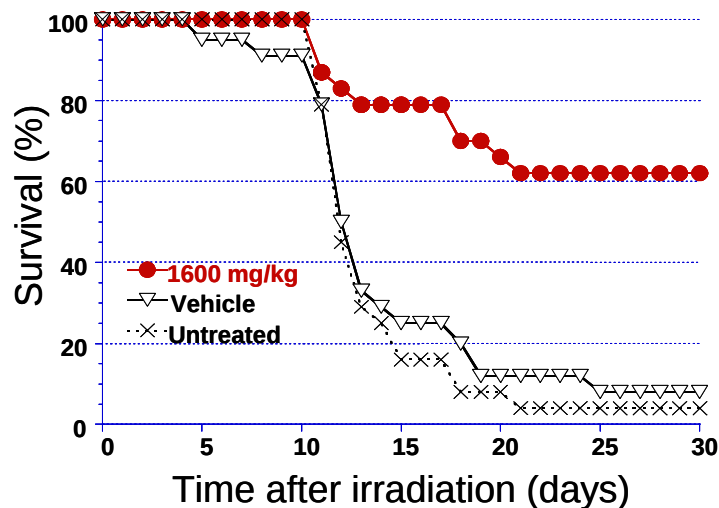


Figure 3: Survival in female B6D2F1 mice exposed to whole-body gamma radiation (11.0 Gy). 5-AED in PEG-400 vehicle was administered by oral gavage in sesame oil vehicle 24 h before irradiation. Survival in the 5-AED treated group was significantly different from survival in the control groups ($p < 0.05$). From data presented in [Whitnall 2002b].

hematopoietic syndrome, basic hematology is done to assess effects on numbers of circulating blood elements and hematopoietic progenitors in blood-forming tissue. Non-Good Laboratory Practice (non-GLP) toxicity studies (clinical chemistry, histopathology, behavior) are performed to detect possible roadblocks to further development. Other assays may be performed to confirm hypotheses about mechanism, depending on what is known about the particular substance being tested. Figure 4 shows an example of a flow cytometric analysis of circulating blood cells after 5-AED administration and whole-body gamma-irradiation.

6.0 DRUG DEVELOPMENT

If a decision is made to advance a compound into a full drug-development process, a formal partnership with a pharmaceutical company is contemplated to facilitate Food and Drug Administration (FDA) interactions, collaborate in studies with large mammals and GLP pharmacology/toxicology assessments, and to fulfill FDA requirements for manufacturing standards and clinical trials. Meetings are requested with the FDA for Pre-Investigational New Drug (Pre-IND) guidance. Further guidance is sought from appropriate Department of Defense (DoD) agencies. Because it would be unethical to perform efficacy trials in humans to demonstrate reduction or prevention of serious or life-threatening radiation injury, efficacy trials for FDA approval are performed under the “Animal Efficacy Rule.” For radiation countermeasures, non-human primates are the appropriate model for pivotal efficacy trials. Initial experiments in non-human primates typically address alleviation of radiation-induced neutropenia and thrombocytopenia, as illustrated by the beneficial effects of 5-AED in this model [Stickney 2004]. Because the FDA will rely on animal experiments to prove efficacy, there is an emphasis on understanding the pathophysiological mechanisms of radiation injury and its amelioration or prevention by the product. This will provide assurance that the efficacy data from studies in animals can be applied to humans [Food and Drug Administration 2002]. Accordingly, a countermeasure that is being prepared for an FDA application will undergo detailed mechanistic studies at the cellular and molecular levels. In the

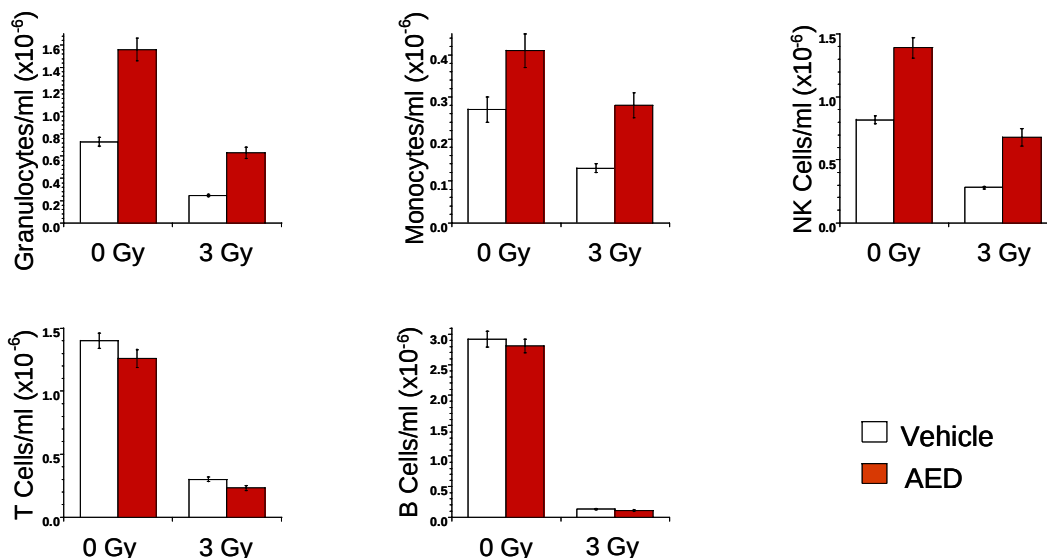


Figure 4: Circulating cells in mice by flow cytometry 4 days after whole-body gamma-irradiation. 5-AED injected sc 24 h before irradiation. The 5-AED effect was significant ($p < 0.05$) for innate immune system cells (granulocytes, monocytes, and NK cells). From data presented in [Whitnall 2001].

case of 5-AED, we are examining effects on hematopoietic cytokines [Grace 2004], functional activation of mature immune cells [Whitnall 2002a], modulation of apoptotic signaling pathways, and the role of specific hematopoietic niche cell lineages, as discussed previously [Whitnall 2000].

7.0 CURRENT CLASSES OF COUNTERMEASURE CANDIDATES

Below are listed some of the most promising compounds in AFRRI's portfolio of radiation countermeasure candidates, along with our partners in evaluating and developing these substances.

- 5-Androstenediol (5-AED), lead candidate (Hollis-Eden Pharmaceuticals)
- Soy isoflavones
- Vitamin E-related compounds (Yasoo Health)
- Phenylacetate, phenylbutyrate, EGCG (late effects)
- Benzyl styryl sulfones (Onconova Therapeutics)
- CpG oligonucleotides (Dennis Klinman, FDA)
- Superoxide dismutase mimetics (Eukarion)
- Statins (Martin Hauer-Jensen, University of Arkansas)
- Dipeptidyl peptidase inhibitors (Point Therapeutics)
- Truncated flagellin (Andrei Gudkov, Cleveland Clinic, Cleveland BioLabs)
- Dietary supplements and/or drugs (Humanetics)

8.0 CONCLUSIONS

Because countermeasure candidates come to us pre-screened by other laboratories, it is rare for a compound to be eliminated quickly from consideration based on our prioritization or baseline assessment evaluations. The ensuing research programs devoted to each substance can consume considerable time and resources. We plan to expand our testing program to better accommodate a growing list of attractive compounds. Our experience with 5-AED has demonstrated the feasibility of developing useful radiation countermeasures with extremely low toxicity. AFRRI's interactions with private industry, academic and government laboratories, and other government agencies have been fruitful in terms of providing research opportunities, leveraging resources, and dealing with regulatory requirements. Given the variety of promising compounds with differing mechanisms of action entering our program, we are optimistic that a number of safe and effective countermeasures will be approved for use in humans.

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REFERENCES

- [Araneo 1995] B. Araneo, R. Daynes. Dehydroepiandrosterone functions as more than an antiglucocorticoid in preserving immunocompetence after thermal injury, *Endocrinology* 136: 393-401.
- [Armed Forces Radiobiology Research Institute 2003] Armed Forces Radiobiology Research Institute. Medical Management of Radiological Casualties, <http://www.afrrri.usuhs.mil/www/outreach/mmresources.htm>
- [Ben-Nathan 1991] D. Ben-Nathan, B. Lachmi, S. Lustig, G. Feuerstein. Protection by dehydroepiandrosterone in mice infected with viral encephalitis, *Arch. Virol.* 120: 263-271.
- [Ben-Nathan 1999] D. Ben-Nathan, D.A. Padgett, R.M. Loria. Androstenediol and dehydroepiandrosterone protect mice against lethal bacterial infections and lipopolysaccharide toxicity, *J. Med. Microbiol.* 48: 425-431.
- [Carr 1998] D.J. Carr. Increased levels of IFN-gamma in the trigeminal ganglion correlate with protection against HSV-1-induced encephalitis following subcutaneous administration with androstenediol, *J. Neuroimmunol.* 89: 160-167.
- [Daigle 1998] J. Daigle, D.J. Carr. Androstenediol antagonizes herpes simplex virus type 1-induced encephalitis through the augmentation of type I IFN production, *J. Immunol.* 160: 3060-3066.
- [Elliott 2002] T.B. Elliott, I. Brook, R.A. Harding, S.S. Bouhaouala, S.J. Peacock, G.B. Knudson. *Bacillus anthracis* infection in irradiated mice: susceptibility, protection, and therapy, *Mil Med* 167: 103-104.
- [Food and Drug Administration 2002] Food and Drug Administration. New Drug and Biological Drug Prod-

ucts; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible, Federal Register 67: 37988-37998.

[Grace 2004] M.B. Grace, C.M. Chang, V.K. Singh, C.B. McLeland, C.E. Inal, W.E. Jackson, III, M.H. Whitnall. *In vivo* induction of cytokine mRNA and protein in mice by the radioprotectant steroid 5-androstenediol, Blood 104: 142b.

[Loria 1992a] R.M. Loria, D.A. Padgett. Mobilization of cutaneous immunity for systemic protection against infections, Ann. N.Y. Acad. Sci. 650: 363-366.

[Loria 1992b] R.M. Loria, D.A. Padgett. Androstenediol regulates systemic resistance against lethal infections in mice, Arch. Virol. 127: 103-115.

[Loria 1996] R.M. Loria, D.A. Padgett, P.N. Huynh. Regulation of the immune response by dehydroepiandrosterone and its metabolites, J Endocrinol 150 Suppl: S209-220.

[Loria 2002] R.M. Loria. Immune up-regulation and tumor apoptosis by androstene steroids, Steroids 67: 953-966.

[Rasmussen 1992] K.R. Rasmussen, M.C. Healey. Dehydroepiandrosterone-induced reduction of *Cryptosporidium parvum* infections in aged Syrian golden hamsters, J. Parasitol. 78: 554-557.

[Stickney 2003] D.R. Stickney, C. Dowding, C.L. Reading, N. Onizuka-Handa, C. Ahlem, A. Garsd, J. Frincke. HE2100 protects irradiated rhesus monkeys against "hematopoietic syndrome", Blood 102: 9a.

[Stickney 2004] D.R. Stickney, C. Dowding, A. Garsd, M.H. Whitnall, J. Frincke. HE2100 and HE3204 protect rhesus macaques from radiation-induced myelosuppression, Abstracts, Annual Meeting of the European Society for Radiation Biology, Budapest: 264.

[Waselenko 2004] J.K. Waselenko, T.J. MacVittie, W.F. Blakely, N. Pesik, A.L. Wiley, W.E. Dickerson, H. Tsu, D.L. Confer, C.N. Coleman, T. Seed, P. Lowry, J.O. Armitage, N. Dainiak. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group, Ann Intern Med 140: 1037-1051.

[Whitnall 2000] M.H. Whitnall, T.B. Elliott, R.A. Harding, C.E. Inal, M.R. Landauer, C.L. Wilhelmsen, L. McKinney, V.L. Miner, W.E. Jackson, III, R.M. Loria, G.D. Ledney, T.M. Seed. Androstenediol stimulates myelopoiesis and enhances resistance to infection in gamma-irradiated mice, Int. J. Immunopharmacol. 22: 1-14.

[Whitnall 2001] M.H. Whitnall, C.E. Inal, W.E. Jackson, III, V.L. Miner, V. Villa, T.M. Seed. *In vivo* radio-protection by 5-androstenediol: Stimulation of the innate immune system, Radiat. Res. 156: 283-293.

[Whitnall 2002a] M.H. Whitnall, V. Villa, J. Benjack, V.L. Miner, T.M. Seed, W.E. Jackson, III. Effects of the novel systemic radioprotectant 5-androstenediol on phagocytosis and oxidative burst in monocytes and granulocytes from mice exposed to whole-body gamma-irradiation, Abstracts, Annual Meeting of the Radia-

tion Research Society 49: 117.

[Whitnall 2002b] M.H. Whitnall, C.L. Wilhelmsen, L. McKinney, V. Miner, T.M. Seed, W.E. Jackson, III. Radioprotective efficacy and acute toxicity of 5-androstenediol after subcutaneous or oral administration in mice, *Immunopharmacol. Immunotoxicol.* 24: 595-626.

[Whitnall 2005] M.H. Whitnall, V. Villa, T.M. Seed, J. Benjack, V. Miner, M.L. Lewbart, C.A. Dowding, W.E. Jackson, III. Molecular specificity of 5-androstenediol as a systemic radioprotectant in mice, *Immunopharmacol. Immunotoxicol.* 27: 1-18.