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Article

A Defined Pathomechanism for Acute Radiation Syndrome Death and a Three Drug Regimen to Prevent It

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Abstract

Death from Acute Radiation Syndrome (ARS) has been a long-standing threat. The current, heightened risk of a nuclear event, e.g., a conflict bomb, terror bomb, reactor core dispersion, or recurrent exposure to medical radiation, would all benefit from a systemic treatment to reduce or eliminate ARS death. This study utilizes a step-wise progression to i) identify why lethally irradiated mice die from ARS, and ii) identify a multidrug regimen, administered before or after irradiation, that prevents or treats ARS pathologies to significantly suppress or eliminate ARS death. Lethal, blood-borne, *E. coli* septic infection was found in 97% of near-death, irradiated mice; this observation was consistent with the numerous breaches observed in GI histology showing broken and breached GI epithelium and GI muscularis externa. Our study found i) a new and clear explanation of why irradiated mice die from ARS, ii) identified two drugs (PrC-210, ciprofloxacin), which administered minutes pre-radiation conferred 100% survival benefit, or 56% when administered a day after irradiation, and iii) a three drug regimen (PrC-210, ciprofloxacin, GCSF) that conferred 92% survival benefit when administered 1-2 days after radiation. The drug regimens can be “field-deployed” to field staging areas as well as to home medicine chests, to enable simple, widespread use of the regimen in the face of radiation threat.

Keywords: ROS-scavenger; jejunal toxicity; nuclear; sepsis; GCSF

1. Introduction

Burns associated with radiation exposure were first described by Tesla after he exposed his hand to x-rays in 1896 [1], but systemic illness and organ failure following radiation exposure were not described in detail until after the Hiroshima and Nagasaki bombings in August, 1945 [2,3]. A Japanese woman, Midori Naka, who was present in Hiroshima, was the first human in 1945 whose death was attributed to what was then referred to as “Atomic bomb disease” [4]. In the 80 years since, this widespread set of human post-radiation organ toxicities has been known as radiation sickness, and more recently as acute radiation syndrome (ARS) [5]. The panoply of organ failure seen after exposure to a lethal ionizing radiation dose has been described following many human exposures to radiation, including Hiroshima/Nagasaki, i.e., through the Atomic Bomb Casualty Commission [5], Chernobyl [6], Fukushima [7], as well as more limited examples of employee exposures to lethal or sublethal radiation doses [8,9].

The organ failure that typically precedes ARS death is principally seen in bone marrow and gastrointestinal sites at radiation doses of 1-9 Gy [10,11], which with successful pre- or post-radiation treatment, could be survived. Neurovascular failure in ARS is typically seen at far higher radiation doses (50 Gy) that are not survivable. In humans, the gastrointestinal epithelium is normally replaced every 3-5 days, so radiation-induced apoptosis of GI epithelial stem cells can lead to significant

denuded tissue sites. Radiation-induced death of bone marrow stem cell populations leaves humans with little ability to address any infectious agent post-radiation.

Human risk of radiation exposure, possibly catastrophic in proportion, has steadily risen and has never been as high as today [12]. Multiple world events, including shelling of nuclear power plants in Ukraine [13], and the U.S. announcement to resume nuclear weapons testing after a 33 year hiatus [14], constitute a clear escalation in nuclear risk. Therefore, a field-ready drug regimen that is able to protect civilian and military personnel, before and especially after any radiation event, has never been greater.

A substantial U.S. government infrastructure has been assembled over the past decades [15,16] to study and strategize responses to enable survivor support following anything from accidental radiation spills to no-warning nuclear attack from international aggressors [12].

The first example of systemically administered “radioprotection” was seen in 1949 following systemic administration of the thiol-containing amino acid cysteine to mice immediately before whole-body irradiation [17]. Countless strategies have since been pursued world-wide in an attempt to identify both pre-radiation-administered “radioprotectors” [18,19] and post-radiation-administered “radiomitigators” [20,21]. The list is long, expensive, with little or no successes.

Our goal in this study, rather than again describe a series of toxicities observed in mammals exposed to lethal radiation, was to identify the cause of death in lethally-irradiated mammals, here outbred mice, and by so-doing, enable a targeted therapeutic regimen that specifically addressed, or ideally suppressed to background, the identified ARS death patho-mechanism. Our goal was to create a likely multi-drug regimen that is “field-deployable,” wherein the “field” represents *both* high-risk military conflict sites, but also home medicine chests, where at-risk soldiers and civilians can administer a regimen themselves, either i) minutes before, or ii) if they survive the thermoblast, a day or days after a nuclear event, to achieve up to 100% “radioprotection” (administered before) or the best possible (up to 92%) “radiomitigation,” when administered after irradiation. Analyses of digital histologic images of gastrointestinal damage following lethal whole-body irradiation of mice taken in our earlier study [22] led us to an hypothesis that considered widespread septic infections in irradiated animals. Pursuit of this hypothesis resulted in i) a confirmed ARS death patho-mechanism, ii) a two-drug regimen, taken minutes before irradiation, that confers a 100% survival benefit, and iii) a three-drug regimen, taken 24 hr after irradiation, that confers a 92% survival benefit to mice administered an otherwise 96% lethal dose of whole-body radiation.

2. Results

2.1. Mouse Irradiation, ROS Production and GI Degradation

We irradiated 25 outbred ICR mice with 8.25 Gy of 320 keV x-rays; the mice were returned to cages and observed over the next 30 days (Figure 1). By observation, the mice developed external signs of Acute Radiation Syndrome, which included i) hunched posture, ii) absence of movement in a setting with cage-mates, iii) ragged coat appearance, and iv) cold to touch when picked up, v) death. The 8.25 Gy dose of x-rays was lethal to 96% of the irradiated mice in the following 24 days.

In Figure 2, we saw that single, systemic doses of the PrC-210 aminothiols ROS-scavenger conferred: i) 100% survival against an otherwise 100% lethal dose of Cs¹³⁷ gamma irradiation when administered IP (intraperitoneally) 15-30 min before irradiation [22], or ii) 44% survival benefit against a 96% lethal dose of x-ray gamma irradiation when administered IP 24 hr after irradiation [23]. In ongoing experiments (data not shown, manuscript in preparation), using intravenous injection into irradiated mice (8.25 Gy) of a coelenterazine derivative [24] to externally image ROS production in irradiated mouse organ sites, we saw three peaks of ROS production in post-irradiation ICR mice, i) during the irradiator-ON time, ii) at 12 hr post-irradiation, and iii) at 144 hr post-irradiation. All three ROS peaks were reduced to background in mice that received systemic PrC-210 either 30 min before [peaks i) and ii)] or 24 hr after irradiation [peak iii)].

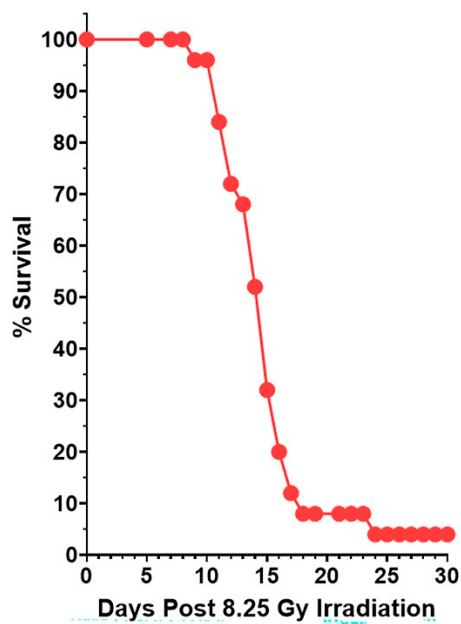


Figure 1. Post-irradiation death following Acute Radiation Syndrome. Twenty-five female outbred ICR mice were irradiated with an 8.25 Gy dose of 320 keV x-rays. Mice were observed over the next 30 days and deaths were recorded.

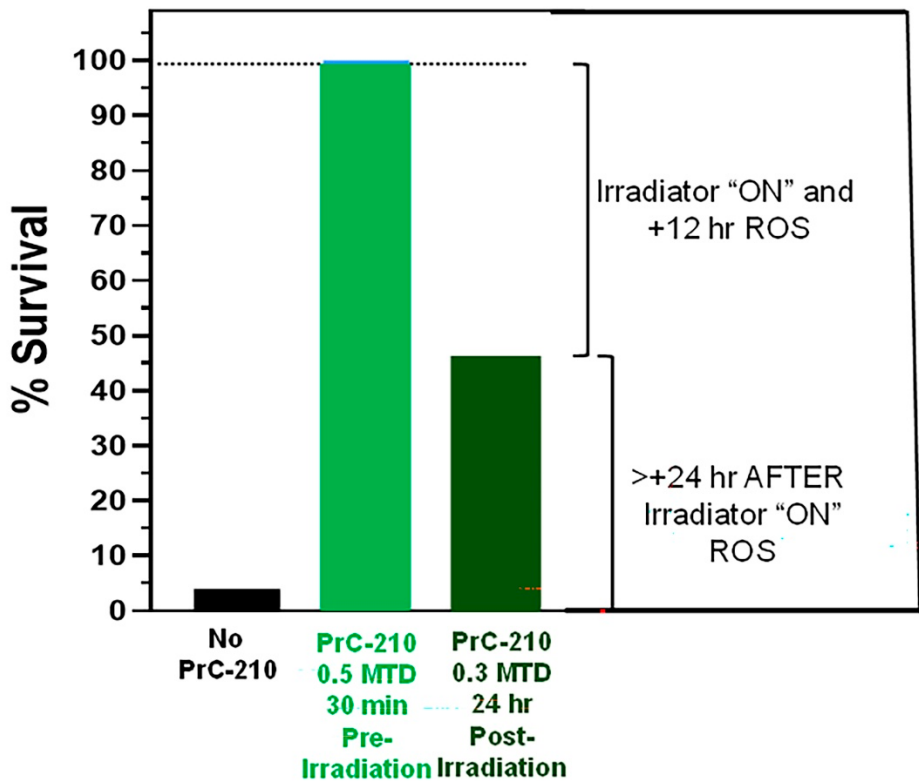


Figure 2. PrC-210 suppression or mitigation of radiation-induced death in ICR mice. Single, systemic doses of PrC-210 were administered either: i) IP (0.5 MTD, 262 mg/kg, 30 min before an LD₁₀₀ dose of Cs¹³⁷ radiation (22), or ii) IP (0.3 MTD, 157 mg/kg, 24 hr after an LD₅₀ dose of 320 keV x-rays (23). Mice were observed over the next 30 days and deaths were recorded. Data are used from indicated references with publisher permission.

In the above-mentioned, early ROS production images of irradiated mice, with a goal of understanding which organs experienced significant radiation-induced ROS damage following lethal irradiation, we analyzed ROS produced from sites over the gastrointestinal tract. Because of the critical roles of GI sites in water and nutrient absorption, as well as its role as a huge repository of gut bacterial flora, this was a primary site of study. Jejunal tissue segments were removed from the same site in irradiated mice on day 14 post-irradiation (see Methods), formalin fixed, H&E stained, and studied by white light microscopy (Figure 3A). The observations of jejunal histology in these mice included: i) (bottom panel) in unirradiated ICR mice, jejunal villi, lamina propria, and muscularis externa were intact and normal, ii) (top panels) in irradiated mice, all jejunal elements, including villar structure and number, lamina propria, and most importantly muscularis externa integrity and intactness were severely degraded; there were multiple tissue gaps in both the villi and the muscularis externa (top panel enlarged images) that would allow leakage of any gastrointestinal lumen contents into the mouse abdominal cavity, and iii) (middle panel) jejuna from mice that received a single 0.3 MTD PrC-210 dose at +24 hr post-irradiation contained largely normal villar structure and density, and *no* detectable gaps or breaks in the muscularis externa capsid wall. Though these images are from jejunal samples, colon histology samples from the same mice showed similar conclusions. Consistent with the histology images, when we analyzed homogenates prepared from like jejunal segments from the same mice (Figure 3B), we saw large elevation of jejunal caspase 3,7 levels in irradiated mice, and suppression of the caspase 3,7 death marker essentially to background ($P=0.004$) in mice treated with the single PrC-210 dose. In plasma from these mice (right caspase panel), the statistically lower level of caspase 3,7 was maintained through the six days post-irradiation where blood samples were collected.

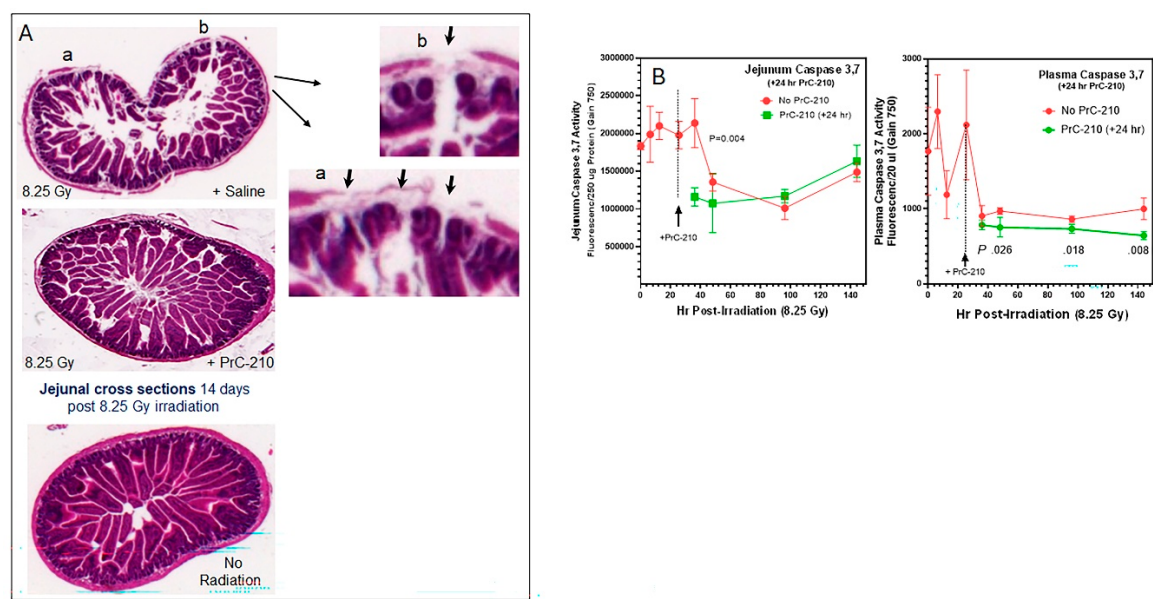


Figure 3. Radiation-induced cell death in mouse jejunum tissue. (A) A two cm segment of jejunum was removed from euthanized mice (4 cm below the gastric/jejunum junction) 14 days following irradiation. H & E histology images showed radiation-induced jejunal villi and jejunal wall breeches (a,b), which were not seen in unirradiated or PrC-210-treated mice. (B) At the indicated post-irradiation timepoints, jejunum segments were removed, rinsed, and then homogenized. Blood plasma was also collected from the same mice. At the indicated timepoints, levels of the caspase 3,7 cell death biomarker were quantified in both the jejunal tissue homogenates and blood plasma recovered from the same mouse. Jejunum caspase 3,7 death marker level was markedly reduced in jejuna of mice injected with PrC-210 24 hr after irradiation ($P=0.004$). Likewise, blood plasma levels of caspase 3,7 were reduced following PrC-210 administration.

2.2. Acute Radiation Syndrome Blood Sepsis and Death

After seeing the presence of breaches in the muscularis externa GI capsid in the irradiated mice, we reasoned that this could provide both i) a pathway for escape of GI floral bacteria, and ii) a patho-mechanism to explain deaths in Acute Radiation Syndrome by septic infection. To test this hypothesis, we irradiated a large group of ICR mice and then euthanized and cultured sterily-drawn blood from the mice at timepoints after they received a 96% lethal dose of whole-body radiation. In Figure 4A, we were startled to find blood borne microorganism CFUs in 100 μ l of individual mouse bloods as early as 2 days after the 8.25 Gy whole-body irradiation. CFU levels in bloods rose exponentially in mice in the first 10 days post-irradiation in which we drew the bloods, basically achieving uncountable “lawns” on blood agar plates by 9-10 days following irradiation. Notably, the first mice die on days 9-10 following irradiation from observable Acute Radiation Syndrome (Figure 1). Over the course of three following experiments, each including 8.25 Gy irradiation of untreated ICR mice, 51 mice were identified in our twice-daily cage inspections to be within mins-hrs of death from apparent Acute Radiation Syndrome (Figure 4B). Sterile blood was collected from each mouse, and 100 μ l of blood or 100 μ l of a blood serial dilution, was spread on blood agar plates. In 49 of 51 mice, we observed either CFU lawns, or countable CFUs in serially diluted blood. Serial dilutions, generally out to 1 million-fold, yielded CFU/ml mouse blood values in the near-death mice of >10 million CFUs/ml. Two near-death mice, 1C-2 and X1A, contained zero CFUs in 100 μ l of their blood.

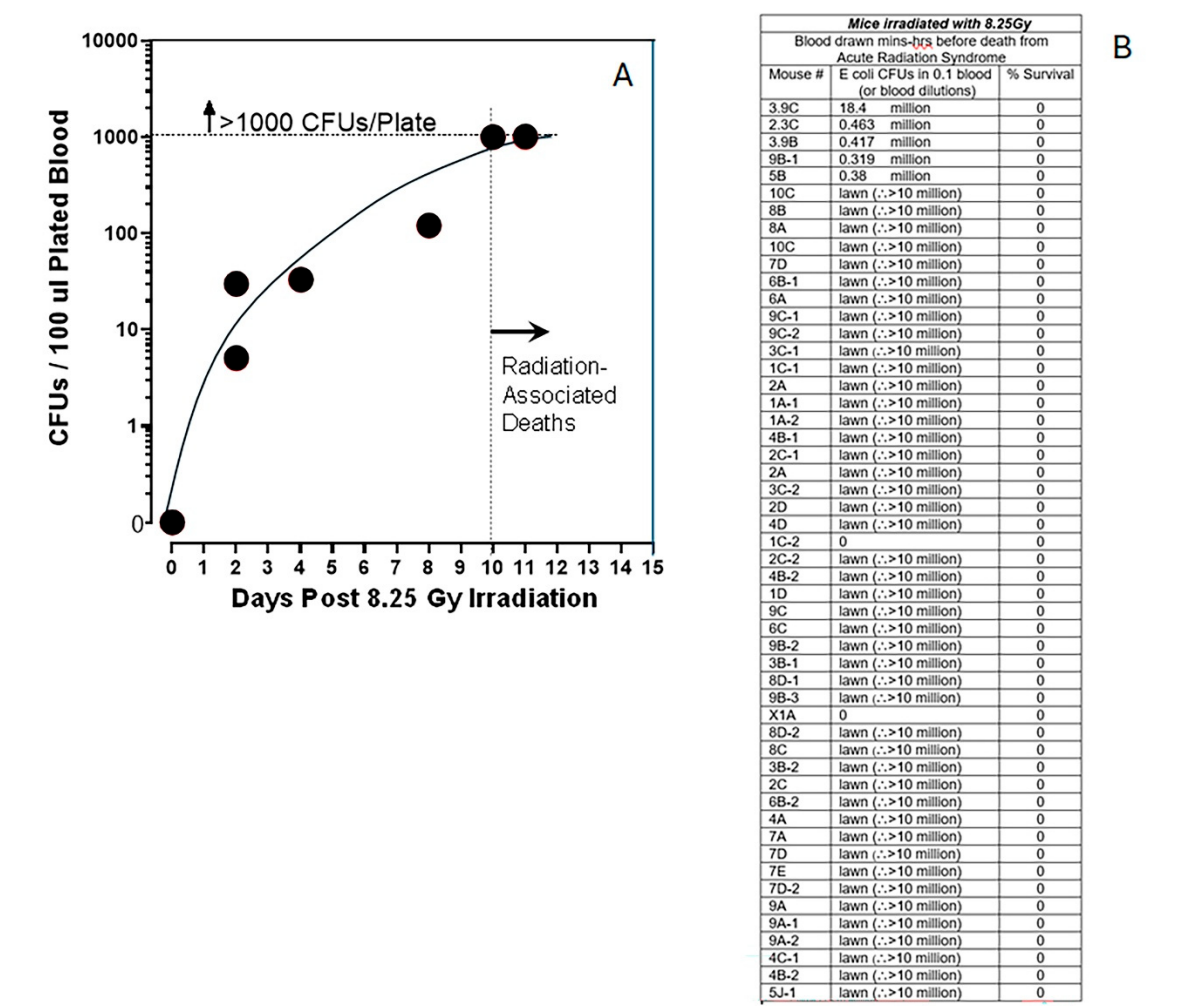


Figure 4. Bloodborne septic micro-organism infection in irradiated mice in the days following 8.25 Gy irradiation. (A) 100 μ l of sterily-collected blood from irradiated mice on the indicated days post-irradiation was plated on blood agar plates and cultured for 24-48 hr at 37°C. Colony counts were recorded. (B) In a large experiment of 8.25 Gy-irradiated mice, 51 mice were euthanized at the point where they were observed to be

within 1-3 hr of death from Acute Radiation Syndrome, typically 10-13 days post-irradiation (i.e., hunched posture, lack of motion in cage, coat was ragged and unsmooth, body was cold to touch). Sterilely collected blood (100 μ l) was collected and plated on blood agar; in some cases, blood dilutions were also plated to better assess actual colony numbers in 100 μ l of blood.

Only two colony morphologies, types “a” and “b”, were ever observed in the plated bloods from irradiated mice (Figure 5A), and in >99% of cases, only type “a” colonies were seen. If our nascent hypothesis of blood sepsis was correct, then we would expect to find these same colony-type organisms in samplings of normal ICR mouse GI flora. To test this, we sterilely dissected segments of both jejunum and colon from an unirradiated ICR mouse, flushed the luminal contents with sterile PBS into a tube and then plated dilutions of the GI floral microorganisms on blood agar plates (Figure 5B). The colony morphologies in the GI flush samples, to the eye, were identical to the colony morphologies seen in the irradiated mouse bloods. To first identify the organisms, and second determine that irradiated blood and GI flush organisms were the same, a type “a” colony and a type “b” colony from both irradiated blood and GI flush were picked and expanded overnight in Luria broth. Bacterial protein extracts from these bacteria were then prepared and analyzed by MALDI-TOF mass spectrometry in a clinical laboratory setting (<https://www.slh.wisc.edu/>). Figure 5C shows an example in which an experimental colony “a” extract MALDI-TOF mass spectrogram is found to be identical to a library MALDI-TOF mass spectrogram from *E. coli*. A like process was used to determine the colony “b” identity as *Lactobacillus suis*. Final analysis identified *E. coli* and *Lactobacillus suis* in GI flushes and the same organisms found in every CFU-positive blood taken from near-death, irradiated mice.

To determine whether a septic, blood-borne *E. coli* infection, *alone*, could explain Acute Radiation Syndrome deaths in irradiated mice, and if so, what blood-borne *E. coli* load was lethal, an “a” colony was picked and expanded overnight in Luria broth. The overnight culture was then titrated by serial dilution and held at 4°C to preclude further bacterial growth; this yielded cultures of around 1.4 billion *E. coli* cells per ml of broth. Healthy ICR mice then individually received a tail vein injection of 150 μ l of PBS containing 0 to 320 million *E. coli* cells, and the mice were returned to cages and observed. In Figure 6A, we see that death occurred in immunosuppressed mice that received anywhere from 0.3 million to 320 million *E. coli* cells per ml of mouse blood. Immunosuppressed mice had received two IP injections of Cytoxan and two IP injections of prednisone (see Methods) in the 7 days prior to the *E. coli* injection. In ICR mice that did not receive the immunosuppressive regimen, a bolus of 5.4 million *E. coli* cells (i.e., 3.0 million per ml blood) caused neither death nor discernible illness. In the plot shown in Figure 6B, we see that all 49 of the “blood CFU positive” irradiated mice (see Figure 4) contained blood-borne *E. coli* loads that exceeded the minimal number of *E. coli* shown to inflict death, when the *E. coli*, *alone*, were injected into healthy, immunosuppressed mice.

In a first experiment to determine whether the observed radiation-induced *E. coli* sepsis could be pharmacologically suppressed, we administered an oral gavage dose of ciprofloxacin every other day to 8.25 Gy-irradiated mice (Figure 7A) and asked whether it affected the presence of blood-borne *E. coli* in these mice versus irradiated mice that received no ciprofloxacin. For the first eight days following irradiation, there was no discernible *E. coli* in mouse bloods from ciprofloxacin mice versus the exponential increases that were seen in irradiated mice untreated with antibiotic (Figure 7A). However, by day +11 post-irradiation, blood levels of *E. coli* had reached those seen in non-antibiotic treated mice, and in the end, the 30-day survival rate in both groups of mice was the same, 0-5%. In the next experiment, we roughly doubled the ciprofloxacin dose administered to irradiated mice by simply increasing the ciprofloxacin gavage to daily instead of alternate days (Figure 7A vs 7B). When these groups of 20 irradiated mice were carried through 30 days post-irradiation, a 15% survival benefit was observed in the ciprofloxacin mice (Figure 7B).

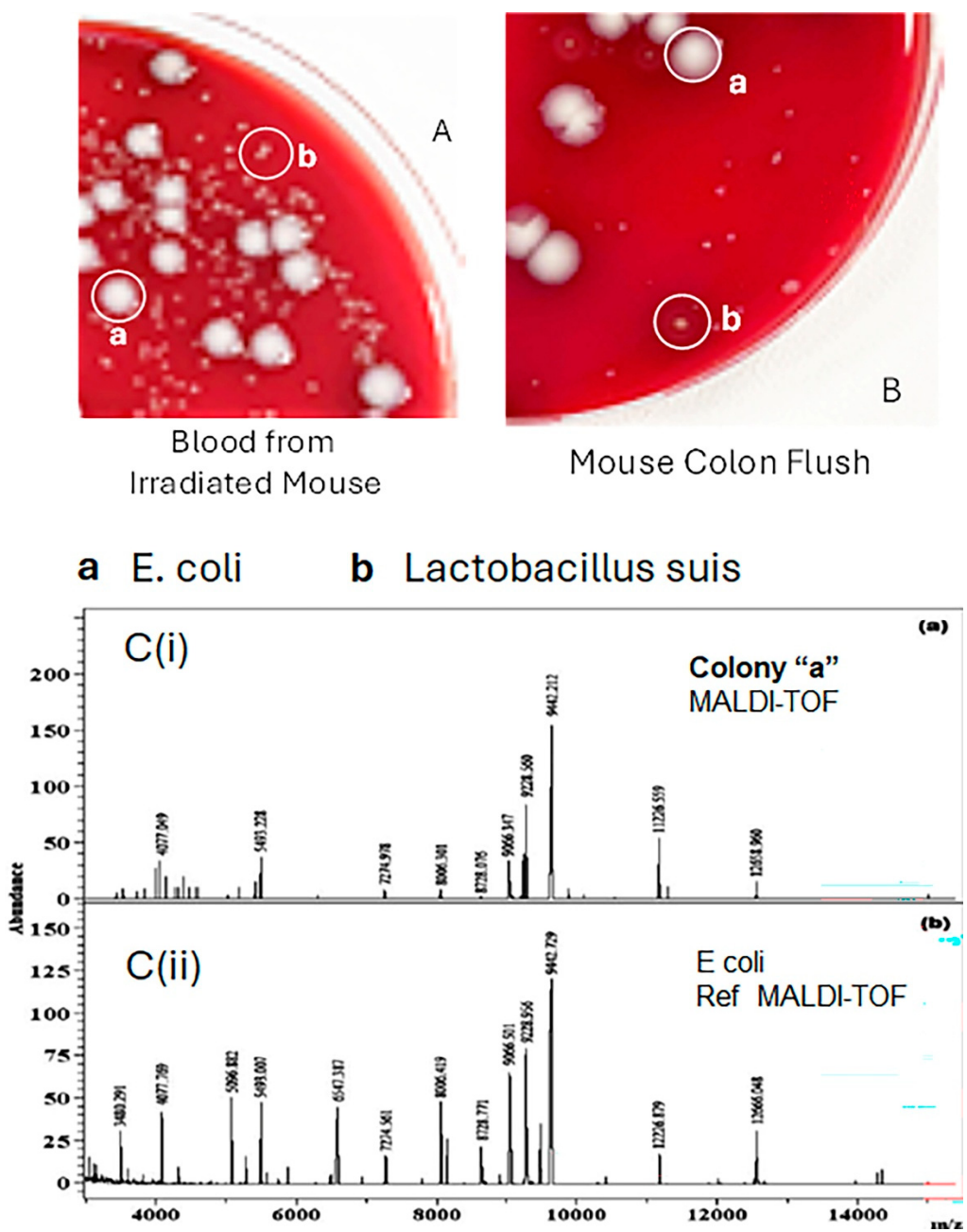


Figure 5. Determine blood micro-organism identity and possible origin in radiation-compromised mouse GI tissue. (A) Blood from an irradiated, near-death (Day +12) mouse was sterilely collected, serially diluted with PBS, and plated on blood agar plates. After 24-48 hr at 37°C, two different colony types were clearly visible, “a” and “b.” (B) The colon from an un-irradiated ICR mouse was sterilely removed, and its contents flushed into a sterile tube using 1 ml of sterile PBS. Serial dilutions of the colon flush were plated on blood agar plates, and photographed after 48 hr at 37°C. (C) Individual colonies (“a” and “b” from both source plates) were expanded in Luria broth and were delivered to a clinical laboratory setting where protein extracts from the expanded colonies were analyzed by MALDI-TOF mass spectrometry and the mass spectrograms were then compared to their library of known bacteria. In the example shown here, the “a” colony mass spectrogram is identical to the library *E. coli* reference mass spectrogram. A like approach was used to identify the “b” colony as *Lactobacillus suis*.

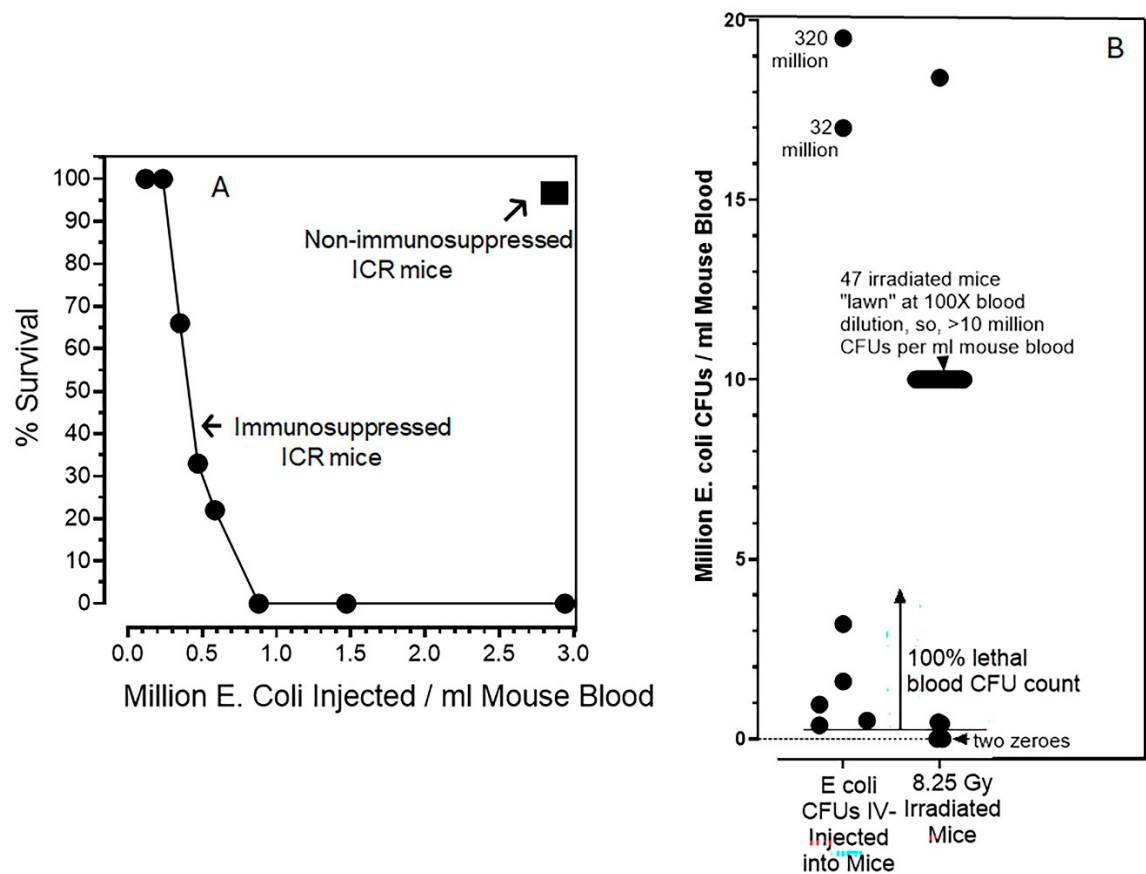


Figure 6. Determination of a lethal septic *E. coli* load when injected IV into healthy, immunocompromised ICR mice. (A) Colony “a” *E. coli* cells, from an irradiated mouse blood sample grown on a blood agar plate, were grown in an overnight Luria broth culture at 37°C. Serial dilutions of the overnight culture were titrated on blood agar plates; the overnight culture was found to contain 1.4×10^9 *E. coli* cells per ml. Aliquots of the overnight culture were diluted in sterile tubes with sterile PBS to yield bacterial suspensions containing 0.3 to 320 million *E. coli* CFUs per 150 μ l. ICR mice which had been immunocompromised (or not) in the week before tail vein *E. coli* injections (see Methods) were individually immobilized in an injection holder, tail veins dilated in warm water, and then injected with 150 μ l aliquots containing known numbers of *E. coli* cells. At least three mice were in each group; injected mice were returned to cages. Mouse survivals in the days following *E. coli* IV injections are shown. (B) Bloodborne *E. coli* CFUs per ml of blood in tail vein-injected, and 51 irradiated mice, are plotted. 49 out of 51 irradiated mouse bloods analyzed contained *E. coli* CFU numbers that were above the minimal “lethal” CFU number determined in the Panel A experiment.

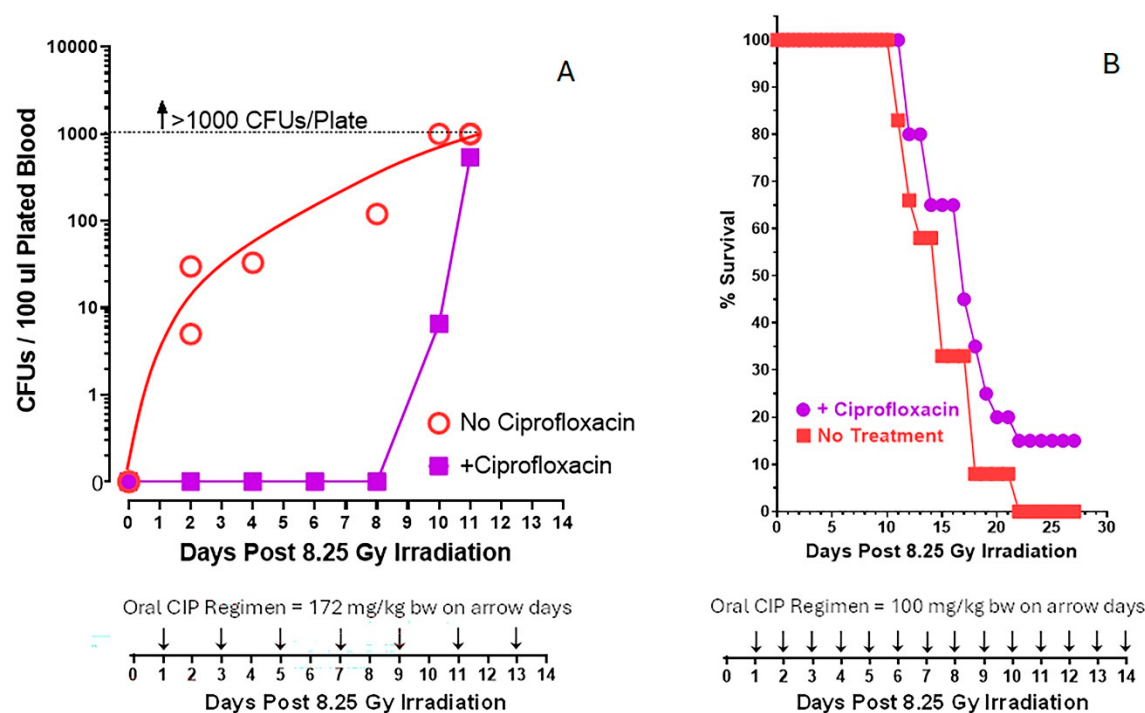


Figure 7. Ciprofloxacin treatment of irradiated mice. ICR mice were all irradiated with 8.25 Gy. (A) Here irradiated mice received an oral gavage dose of ciprofloxacin (172 mg/kg bw) every other day following irradiation. Whereas mouse blood bacterial CFUs were detectable shortly after irradiation in non-ciprofloxacin treated mice (plot taken from Figure 4A), mice which were irradiated but also received alternate day oral ciprofloxacin showed no detectable blood bacterial CFUs through day 8 post-irradiation. After day 8, CFUs rose very rapidly, and none of the mice on this ciprofloxacin dose regimen survived. (B) In a subsequent experiment, groups of 20 mice all received 8.25 Gy irradiation; 20 then received no treatment and 20 received *Daily* oral gavage ciprofloxacin (100 mg/kg) for 14 days following irradiation. With this ciprofloxacin regimen, there was a 15% survival benefit over 30 days.

2.3. A Multidrug Regimen to Suppress Acute Radiation Syndrome Death

In an earlier study from our lab [23], several combined regimens of IP PrC-210 and SC GCSF (Neupogen) were tested to determine what combined survival benefit could be achieved with the two drugs administered beginning at +24 hr post-irradiation. In Figure 8 we see that the two drugs were almost perfectly additive in their survival benefits when dosed in the regimen shown in Figure 8B. The individual survival benefits of 43% (PrC-210) and 45% (GCSF) achieved a profound survival benefit of 88% when administered by their separate delivery routes into groups of 25 irradiated mice.

Present day needs for either a “prevention” regimen against subsequent irradiation or a “treatment” regimen against prior irradiation places a profound emphasis on: i) a “field-ready” drug regimen that could be available through government/military stockpiles as well as “main street” pharmacies to civilian populations, and ii) that multidrug regimen that will confer the greatest survival benefit to at-risk military and civilian populations. To address both needs i) and ii), we undertook a series of radiation survival experiments using multidrug regimens in both “prevention” and “treatment” protocols to identify the best possible field-ready options available to at-risk military and civilian populations.

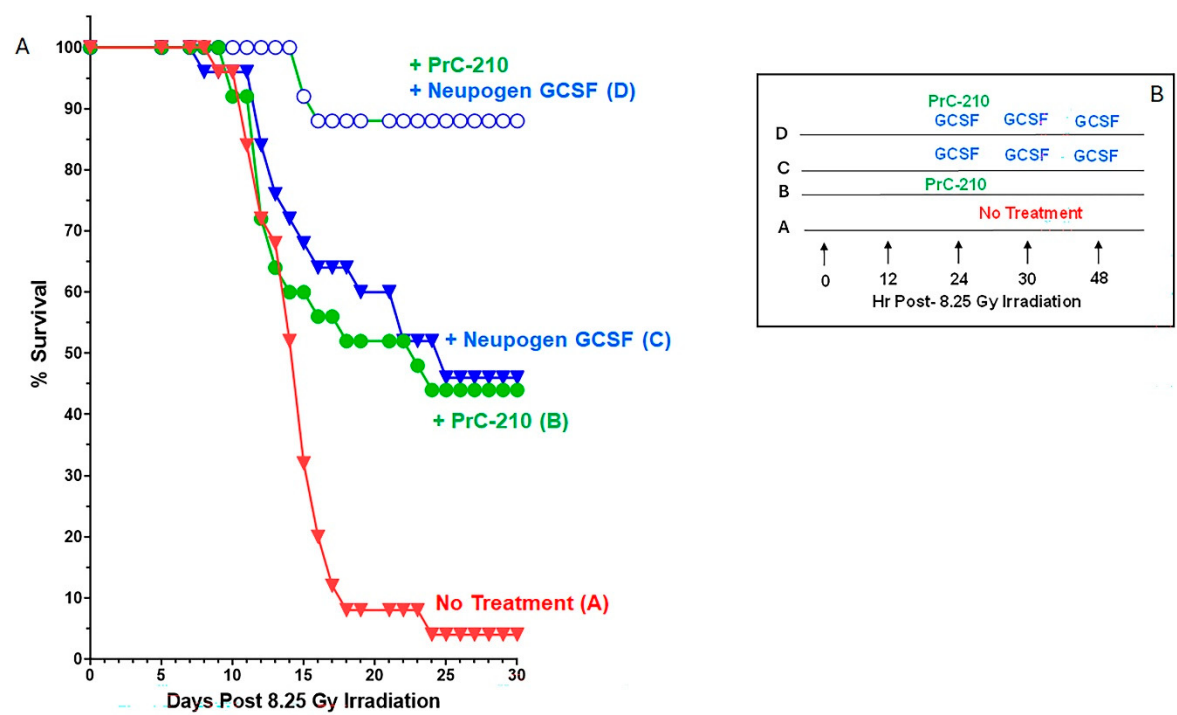


Figure 8. PrC-210 and GCSF-conferred post-irradiation mouse survival. Survival in four groups (25 ICR mice per group) all of which received 8.25 Gy of whole-body irradiation. (A) Schematic illustrating the post-irradiation times at which i) a single IP PrC-210 dose (0.3 IP MTD, 157 mg/kg bw), or ii) three SC doses of GCSF (Neupogen, Amgen) or iii) both drugs were administered to irradiated mice, starting 24 hr after irradiation. (B) Mice were observed twice daily for survival for the 30 days following the 8.25 Gy irradiation.

In a first set of experiments, we sought to optimize the optimum dose of PrC-210 when administered to irradiated mice in a “field-ready” oral dose, or a less “field-ready” SC dose (Figure 9) in both “prevention” and “treatment” settings. In Figures 9-11, we conducted full 30-day survival studies for mice treated as indicated beneath the individual bars, and for concise comparison, the final survival values at +30 days are presented here as simple bars (see Survival Plot insert in Figure 9). The mouse groups each contained an N of 25. In Figure 9 we see 100% survival of mice that received an oral 0.5 MTD (900 mg/kg, this oral MTD dose is from 2010; it was done in “fasted mice”) PrC-210 dose 60 min before a 100% lethal radiation dose. We then tested a range of oral PrC-210 doses (0.075 – 0.3 MTD, i.e., 195-780 mg/kg; a new 2025 oral MTD of 2600 mg/kg for non-fasted mice) administered once at +24 hr post-irradiation. The +24 hr oral PrC-210 dose (0.150 - 0.200 MTD, 390-520 mg/kg) that conferred a maximum survival benefit of 44% (i.e., 48%-4%) compared well with the survival benefits conferred by the optimum SC dose (52%, 0.1 MTD) and the optimum IP dose (43%, 0.3 MTD) shown in Figure 9.

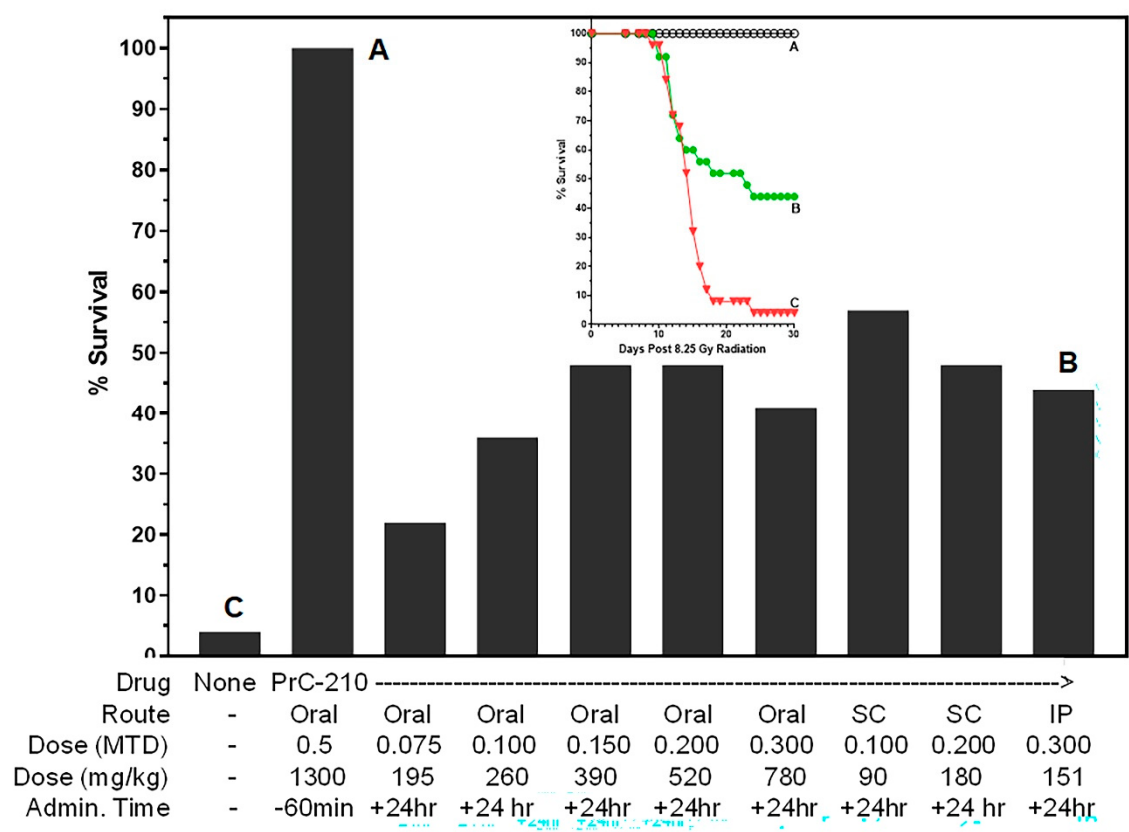


Figure 9. PrC-210-conferred pre-irradiation and post-irradiation mouse survival. Thirty day survival in mouse groups (25 ICR mice per group), all of which received 8.25 Gy of whole-body irradiation. Pre-irradiation PrC-210, IP (30 min before, ref. [22]) or oral (60 min before, ref. [28]) conferred 100% survival against an otherwise 100% lethal radiation dose. Administration of PrC-210, alone, 24 hr post-irradiation, by SC injection or oral gavage also conferred significant survival benefit. Mice were observed twice daily for survival for the 30 days following the 8.25 Gy irradiation.

When the optimum oral PrC-210 dose (0.20 MTD, 520 mg/kg), administered once at +24 hr, was combined with the optimum three-dose SC GCSF (Neupogen) regimen, the survival benefit of 84% (88%-4%) equaled (Figure 10) the previously observed [23] 84% survival benefit seen for IP PrC-210 + GCSF (Neupogen) also shown in Figure 10. Combination of the optimum SC PrC-210 dose (0.10 MTD) with the optimum three-dose SC GCSF (Neupogen) regimen also yielded a high survival benefit of 68%. Substitution of a single injection of pegylated GCSF (Neulasta) at +24 hr for the three injection Neupogen regimen complemented by the single oral PrC-210 dose (0.20 MTD) also yielded a very high survival benefit of 80%.

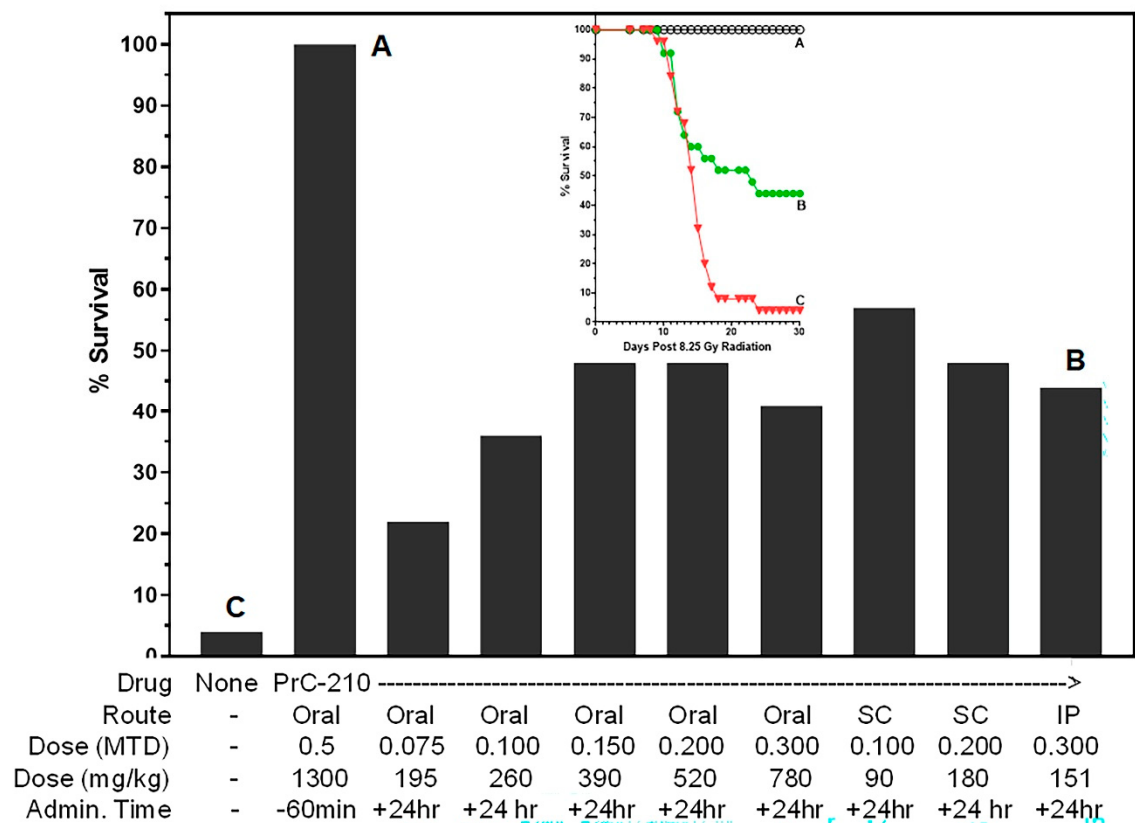


Figure 10. PrC-210 and GCSF-conferred post-irradiation mouse survival. Thirty-day survival in mouse groups (25 ICR mice per group), all of which received 8.25 Gy of whole-body irradiation. Pre-irradiation PrC-210, IP (30 min before, ref. [22]) or oral (60 min before, ref. [28]) conferred 100% survival against an otherwise 100% lethal radiation dose. Administration of PrC-210 alone 24 hr post-irradiation, by SC injection or oral gavage, conferred significant survival benefit. Mice were observed twice daily for survival for the 30 days following the 8.25 Gy irradiation.

In light of the massive E.coli sepsis found in these irradiated mice (Figure 4), and with a 15% survival benefit conferred by daily ciprofloxacin, alone, post-irradiation (Figure 7B), in a final set of irradiation experiments, we assembled a three drug “treatment” regimen (Figure 11) in which daily oral ciprofloxacin was included with the optimum single oral PrC-210 dose (0.20 MTD) and either three-dose Neupogen or one-dose Neulasta regimen, and the outcome basically showed an additional additive survival effect in which the small ciprofloxacin benefit was added to the singular PrC-210 benefit (43%, Figure 9) and the singular Neupogen (44%) or Neulasta benefits. Notably, administration of PrC-210 at +24 hr plus ciprofloxacin also conferred an additive survival benefit (56%; i.e. 60%-4%), and as expected, administration of the single PrC-210 dose at 60 min before irradiation followed by ciprofloxacin conferred the same survival benefit (100%, Figure 11) as that seen when PrC-210 alone was administered at 60 min before irradiation (Figure 9, ref. [28]).

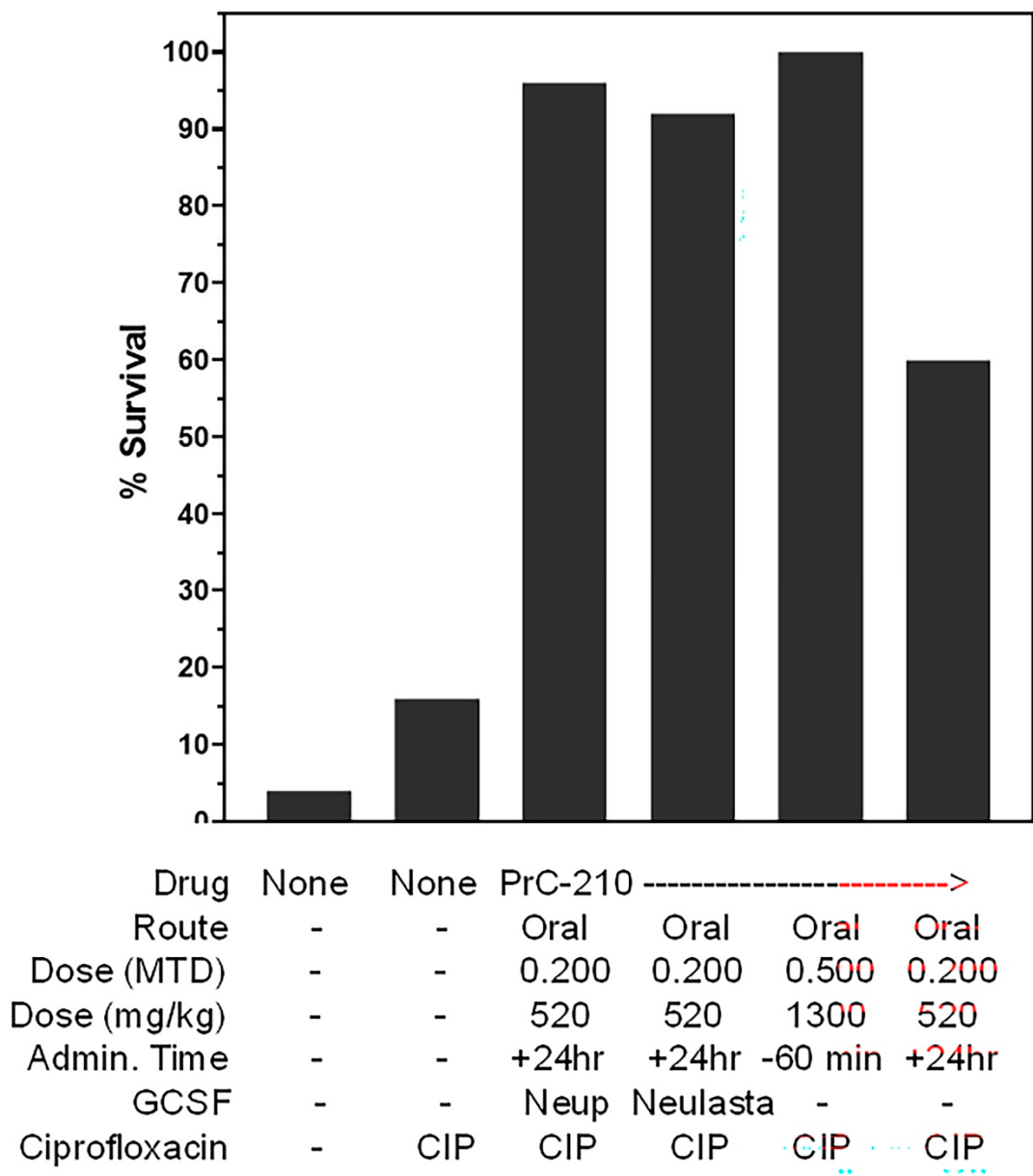


Figure 11. Combined PrC-210, GCSF and ciprofloxacin-conferred post-irradiation mouse survival. Thirty-day survival in mouse groups (25 ICR mice per group), all of which received 8.25 Gy of whole-body irradiation. Pre-irradiation oral PrC-210 plus oral ciprofloxacin regimen, i.e., the “DuoProtect²® Card (Figure 13) conferred 100% survival against an otherwise 96% lethal radiation dose. Oral PrC-210 plus oral ciprofloxacin and SC GCSF (Neupogen) or pegylated GCSF (Neulasta) conferred 92% survival benefit. Mice were observed twice daily for survival for the 30 days following the 8.25 Gy irradiation.

3. Discussion

In this study, we conducted a step-by-step series of analyses i) to identify the reason why lethally irradiated animals die at the end of the Acute Radiation Syndrome pathology progression, and with this knowledge, ii) to identify a multidrug regimen, administered before or after irradiation, that logically prevented or treated the individual pathologies to confer substantial, or complete, protection against ARS death. Nearly as important as the specific drug regimen, was to visualize a means to “field-deploy” the drug regimen elements to field staging areas and home medicine chests, to enable simple, widespread use of the regimen in the face of radioactive threat. ARS is a long-standing, 80+ year threat, and the risk of a significant nuclear event, whether conflict bomb, terror

dirty bomb, reactor core dispersion, or exposure to low dose/long term medical radiation, all would benefit from a simple, systemic treatment to reduce or eliminate radiation risk.

Because ionizing radiation-induced ROS (Reactive Oxygen Species), principally ·OH hydroxyl radical, are responsible for the large majority of radiation-induced cell death [25,26], both during the “beam-ON” time, as well as in mitochondrial damage “ROS waves” at 12 and 144 hr after irradiation (Figure 2), it’s logical that the new PrC-210 ROS-scavenger, which outperformed the 13 other most-cited antioxidants in PubMed [27] by one to several orders of magnitude, conferred significant protection to all organs in these irradiated mammals (Figure 2 and ref. [22]).

Our first observation of blood-borne E coli on day two following lethal irradiation of mice (Figure 4) was surprising. The exponential expansion of the septic bacteria in the irradiated immune-compromised mice in the following days was less surprising. After studying the earlier histology images from irradiated mice taken from multiple sites along the GI tracts in our earlier study [23], and the significant PrC-210 suppression of the observed GI pathology in mice treated either immediately before or 24 hr after lethal irradiation [23], it was clear that breaches in the GI wall integrity in PrC-210-untreated mice (Figure 3B) were common. When we cultured blood from 51 irradiated, near-death mice, we found septic bacteria in 97% of the mice. When we recreated the same IV burden of E coli strain in otherwise healthy, but immunocompromised mice, it was apparent that the bacterial burden seen in the irradiated mouse bloods, *alone*, was 100% lethal to the mice. The observed death of two of 51 mice who had zero blood-borne bacteria, to us is consistent with a Monte Carlo multifactor mortality risk model (see Figure 12) that we previously offered [23] in which multiple, parallel, organ failures in irradiated animals, in aggregate, explains death in the 3% of mice with no blood-borne bacteria.

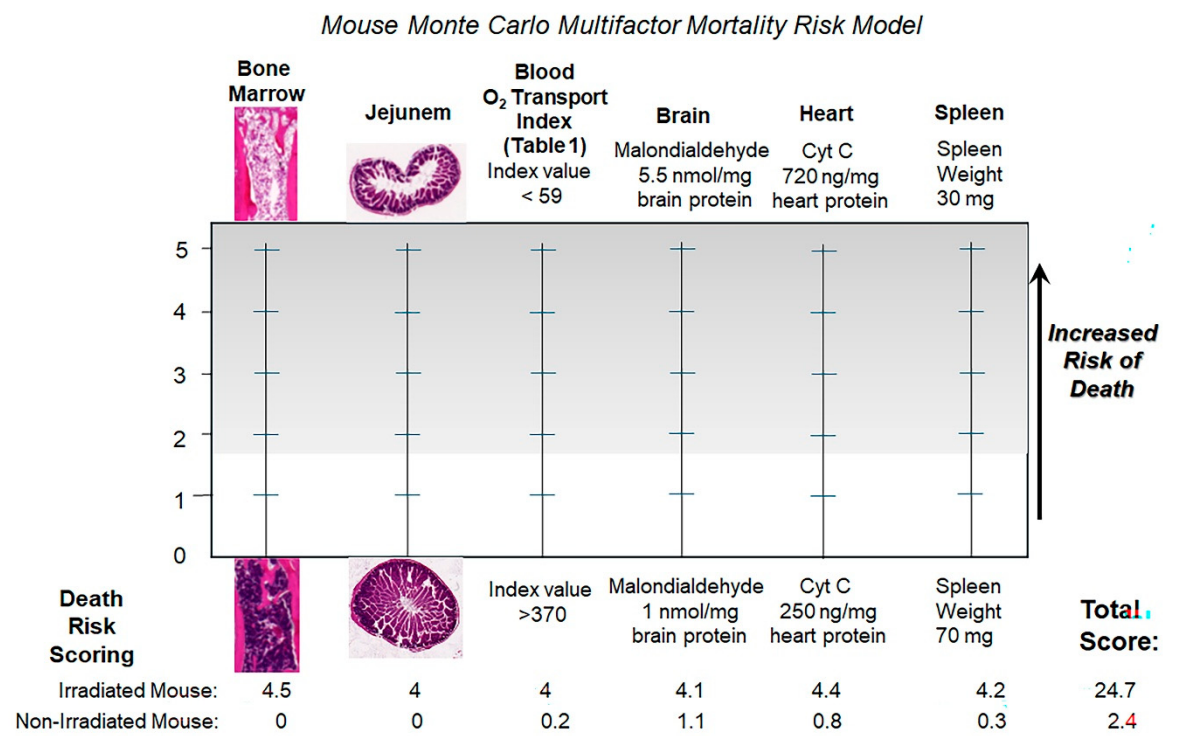


Figure 12. Monte Carlo multifactor mortality risk model for *non-bacterial-sepsis* deaths in irradiated mice. Multiple, parallel, failure of critical organs in the Acute Radiation Syndrome is routinely seen in mice following lethal whole-body irradiation. For the two mice in Figure 4 that showed zero CFUs in their blood cultures at the time of their death, we hypothesize that their deaths are explained by this model of aggregate risk associated with multiple critical organs failing in parallel in lethally irradiated mice. The Figure summarizes primary data originally reported in ref. [23], used here with journal permission.

The 97% occurrence of lethal septic bacteria in irradiated outbred mice resulted from two, required events, i.e., i) GI epithelial degradation and breach of the GI tract wall, and ii) parallel immune suppression of the mice that we saw was “required” (see Figure 6A) to enable *lethal* septic infection. It’s logical then that a three drug regimen in which i) **PrC-210**, administered orally *once* before or after irradiation, sustains the overall integrity of the entire GI tract (see Figure 3) and helps maintain bone marrow density and recovery time [23], ii) **ciprofloxacin**, administered orally daily, here for 14 days, precludes blood expansion of any leaked GI bacteria until both immune function and GI integrity are restored by 14 days, and iii) **GCSF**, administered by subcutaneous injection three times 24-48 hr post-irradiation, which significantly hastens restoration of bone marrow cells [23] and immune infection suppression, together confer 92% survival benefit to irradiated mice (Figure 11).

PrC-210, alone [23,28], or with accompanying ciprofloxacin (Figure 10) conferred 100% survival benefit when taken 60 min before, or 56% survival benefit when taken 24 hr after lethal irradiation. The addition of GCSF to the PrC-210 + ciprofloxacin DuoProtect² regimen clearly provided a profound additional survival benefit (36%), but field availability of an injectable drug, stored at 4°C, is a substantial hurdle to overcome for mass use in a field setting. Figure 13 shows that in addition to, such as, military field use settings, interestingly, the best “field” setting for the three-drug regimen including GCSF would likely be for civilians in their homes. With a 2+ year shelf-life for GCSF when refrigerated, it would be easy for civilians to buy with prescription the three drug regimen with a likely 10-year shelf-life for PrC-210 and ciprofloxacin and a replaceable 2-year dose of GCSF, all of which could be administered by oneself, at home. A person could self-treat any time that there was a perceived or real threat of nuclear exposure, even for survivors of a thermoblast that were located sufficiently distant to the nuclear event, and who then had to deal with fallout and exposures in the hours to days following the nuclear event.

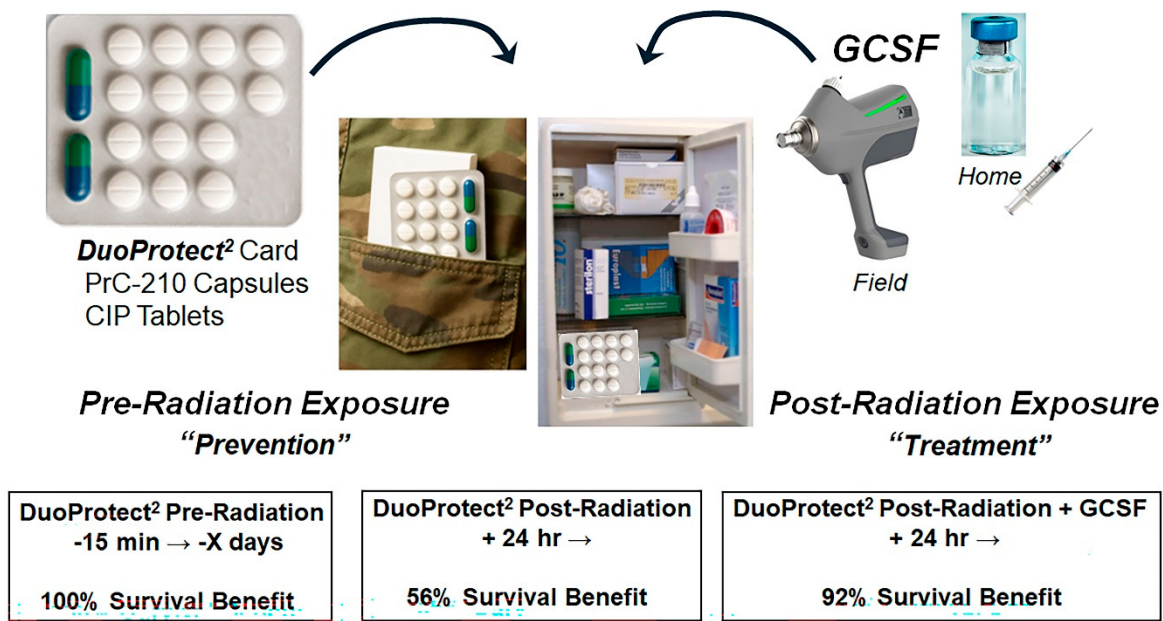


Figure 13. A military and civilian “field-deployed” radiation “Prevention” and “Treatment” drug regimen. The envisioned DuoProtect² card containing PrC-210 oral gel capsules and 14 ciprofloxacin oral tablets in a water- and oxygen-excluding dose card could be easily deployed in both military and civilian settings. The PrC-210 (alone) oral dose, taken 15-30 min before radiation exposure, was previously shown (ref. [28] and Figure 9) to confer 100% survival against an otherwise 100% lethal dose of whole-body radiation. Daily ciprofloxacin in a post-exposure radiation setting would provide additional supportive protection against bacterial infections. Beginning 24 hr after radiation exposure, oral administration of this field-deployed PrC-210 dose, when combined with the DuoProtect² doses of ciprofloxacin, would confer greater than 55% survival benefit (Figure 10), but when combined with a single SC injection of GCSF (eg., Neulasta, Figure 11) would confer 92% combined survival benefit from this three-drug regimen. Field deployment of GCSF from any current manufacturer would

be challenging, but certainly possible for both military, and as importantly, civilian populations, particularly with a 2 yr GCSF shelf-life in a family's home refrigerator.

Agent storage and shelf-life to enable rapid availability to large (millions) of at-risk individuals, is almost as important as the radioprotective efficacy of the agent. To date, chemical degradation of the crystalline PrC-210 HCl salt has been seen only in settings in which both water and oxygen were present. Monitoring the integrity of the PrC-210 thiol is easy; dissolution of crystals in water or methanol, with immediate analysis by mass spectrometry yields a single $n+1$ peak at 149 atomic mass units [29]. Degradation of the thiol to the disulfide yields visible peaks at 295 and 148 amu. Storage of PrC-210 HCl crystals in a single bottle, with over 100 openings over a four-year period, showed no detectable disulfide formation when the bottle was flushed with dry N₂ prior to its resealing. We have formulated PrC-210 HCl crystals in gelatin capsules, and following their oral delivery to mini-swine [30], have observed clear, dose-dependent efficacy as well as clear, dose-dependent toxicity while establishing the mini-swine NOAEL (No Adverse Effect Level) dose, which then provides easy estimation of oral dosing and likely PrC-210 oral NOAEL doses in humans. Dry formulation of PrC-210 crystals/powder in gel capsules in atmosphere-sealed bottles or plastic-foil dose cards would yield easy storage and long term (years) storage in both at-home medicine chest and field-ready storage settings for mass distribution.

In this thorough analysis of the lethal ARS patho-mechanism and then of a multidrug regimen to suppress the lethal ARS organ pathology, we found a new and clear explanation of why lethally irradiated mice die from ARS and then identified two drugs which administered pre-emptively confer a 100% survival benefit, or 56% if after irradiation, as well as a three drug regimen that conferred 92% survival benefit when administered 1-2 days after lethal irradiation. Next studies will pursue non-human primate corroboration of these results and transition of the PrC-210-based drug regimens to human availability and use.

4. Materials and Methods

4.1. Materials and PrC-210

PrC-210 HCl (MW: 220) was synthesized for these studies as previously described [31,32]. ICR (CD-1) mice (female, 25-30 gm) were purchased from Envigo (Madison, WI). Neupogen and Neulasta were purchased from Amgen (Thousand Oaks, CA). Caspase 3,7 ApoOne assay kit were purchased from Promega (Fitchburg, WI). Ciprofloxacin, solvents and other chemicals were purchased from Sigma-Aldrich (St Louis, MO). Blood agar plates were from Diamante Scientific, (Boardman, OH).

4.2. Mouse Studies

All animal experiments complied with international and local animal welfare standards and were approved by the respective regulatory committees. This research was approved by School of Medicine and Public Health Institutional Animal Care and Use Committee at the University of Wisconsin (Protocol #M006610). All procedures were performed in accordance with the Animal Care and Use Policies at the University of Wisconsin. Mice were maintained on a 12 hr light/dark cycle and were provided *ad libitum* water and lab chow (Harlan Teklad 8604).

Unanesthetized mice in a plexiglass pie chamber were irradiated in an Xstrahl CIX3 research irradiator with 300 keV x-rays at 1.37 Gy/min. Thirty min before, or 24 hr after irradiation, mice received a single systemic dose of PrC-210, either by IP (intraperitoneal) injection, SC (subcutaneous) injection, or oral gavage delivery route. The delivery route and individual administered doses of PrC-210 are provided in legends to each figure. As background, the IP MTD (Maximum Tolerated Dose) is 524 mg/kg bw, the SC MTD is 900 mg/kg bw, and the oral MTD, in non-fasted mice, is 2600 mg/kg. The PrC-210 pH 7.2 solution IP injection volume (μ l) is 5.6 times the mouse body weight. The PrC-210 pH 7.2 solution SC injection volume (μ l) is 1% of the mouse body weight. The PrC-210 pH 4.9 solution (i.e., PrC-210 HCl simply dissolved in water) oral gavage volume is 1% of the mouse body

weight. At 24, 30 and 48 hr following irradiation, mice received SC injections of 0.17 mg/kg of G-CSF (Neupogen, Amgen, Thousand Oaks, CA). For Neulasta, mice received a single 1 mg/kg bw SC injection 24 hr after irradiation.

Following drug treatments, mice were returned to cages and observed twice each day for the next 30 days. In mice euthanized hours to days following irradiation, blood was collected and plasma isolated and frozen at -80°C.

4.3. Mouse Organ Damage Biomarker and Imaging

In studies involving isolation of mouse organs, mice were euthanized by CO₂ overdose. A 2 cm segment of jejunum, 4 cm below the stomach:jejunum juncture, was isolated, lumen flushed with caspase buffer, and then homogenized in 1 ml of 4°C caspase buffer using a Polytron homogenizer (ThermoFisher, Chicago, IL) run at full speed for 30 sec. 500 µl of homogenate was transferred to an Eppendorf tube and frozen on dry ice or liquid nitrogen, and stored at -80°C. In some mice, an adjoining jejunum segment was rinsed in buffer and then immersed in 10% formalin. H&E staining, sample sectioning and mounting, and microscopy and scanning of 10X images using an Optika Optiscan10 scanner to generate jpg images was done as described [33]. For sampling of colon flora microorganisms, a colon segment was sterilely dissected out, and its luminal contents flushed into a sterile tube using 1 ml of sterile PBS (phosphate-buffered saline, pH 7.2). Serial dilutions of the colon flush suspension were plated on blood agar plates.

Activated caspase 3 and 7 activity in mouse jejunum homogenates or plasma was determined using the Apo-ONE fluorescent substrate [23] (Promega, Madison, WI). The activated caspase 3,7 assay was performed as follows: Twenty µl of mouse plasma (stored at -80°C) or buffer dilutions of jejunum previously homogenized in caspase buffer (50 mM HEPES, pH 7.4, 100 mM NaCl, 1 mM EDTA, 10% glycerol), were mixed with 50 µL of the undiluted Apo-ONE substrate in the well of a black, opaque, 96 well plate to initiate the 60 min reaction; total reaction volume was 100 µl. Plates were shaken at 175 RPM at 37°C for 60 min. The fluorescent DEVD caspase 3,7 substrate peptide cleavage product was measured using a BMG Clariostar fluorescent plate reader at an excitation wavelength of 499 nm and an emission wavelength of 521 nm. A caspase internal standard was included in each experiment.

For statistical analysis, either the Student's T test was used for simple comparisons between groups, or the Mantel-Cox test was used to compare differences in survival between groups. For correlation analyses, Pearson correlation coefficients ("R") were calculated using Graphpad Prism.

4.4. Mouse Blood Bacterial Analyses

For mouse blood CFU analyses, either healthy or near-death mice following irradiation (i.e., hunched posture, motionless in cage, ragged coat, cold to touch) received a bolus overdose IP injection of pentobarbital (3 mg); when unresponsive, heads were detached by scissors, and blood was collected into sterile tubes. For simple blood CFU screening, 100 µl of blood was spread onto a blood agar plate and inverted plates were incubated at 37°C for 24-48 hr. Plates were photographed and CFUs recorded. In some cases, bloods were diluted up to 1 million-fold in sterile PBS, and 100 µl of each dilution was plated and CFUs counted to give accurate CFU counts per ml of mouse blood. Mouse blood volume was calculated to be 6.4% of the mouse body weight.

To identify the bacteria that composed the only two colony types ever seen in blood from irradiated mice or a colon flush from a healthy ICR mouse, an example of each colony was picked, expanded in Luria broth, and then subjected to MALDI-TOF mass spectrometry [34] at the Wisconsin State Laboratory of Hygiene (<https://www.slh.wisc.edu/>). In studies in which defined numbers of E.coli cells were IV-injected into mice, some of the mice were first immunocompromised as described [35,36]. Briefly, in the week before IV E.coli injections, mice received two IP injections of 100 mg/kg Cytoxan, and two 50 µl IP Injections of 1 mg/kg prednisone (0.5 mg/ml in DMSO:water, 1:10). Immediately prior to E.coli IV tail vein injections, mice were placed into a plexiglass immobilization holder (Braintree Scientific, Braintree, MA), tails were immersed for 10 sec in 105°F tap water. Tail

veins were accessed using 30 g needles on 1 cc syringes, and 150 µl of PBS containing defined numbers (0.3 – 500 million) of *E. coli* cells from titrated overnight cultures was injected as a bolus. Mice were returned to cages and observed for death in the following seven days.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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