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BRIEF REPORT

Are We Ready for a Radiological Terrorist Attack Yet? Report From the Centers for Medical Countermeasures Against Radiation Network

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The events of September 11, 2001, highlighted an ongoing risk from large-scale radiation incidents and emphasized our limited ability to treat radiation injuries. In response, a network of Centers for Medical Countermeasures against Radiation (CMCR) was funded through the National Institute of Allergy and Infectious Diseases. As this program approaches the end of 10 years of funding, the CMCR leadership thought it appropriate to appraise the radiation community of its progress, particularly toward its 2 main goals: first, to develop after-the-fact dosimetry, and second, to develop medical countermeasures against acute and late effects of radiation exposure.

Of the currently available methodologies for radiation biodosimetry of individuals, the existing "gold standard" technique is the dicentric analysis, but this time-consuming assay would not be easily scalable to an event involving, potentially, millions of personnel. Through the efforts of the CMCR network, several techniques now are becoming available for high-throughput biodosimetry: for example, the RABiT approach (Rapid Automated Biodosimetry Technology), which uses a single drop of blood from a fingerstick and is able to process up to 30,000 samples per day (1); genomic signature identification that is highly accurate in predicting dose up to 7 days after irradiation (2); and electron paramagnetic resonance dosimetry, which uses teeth or nails in situ that can give an immediate readout of estimated dose (3).

In contrast, the complex mechanisms that underlie the acute and delayed responses to radiation have made medical countermeasure development painfully slow. Furthermore, the CMCR program has been charged with developing agents that will decrease mortality when

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administered no earlier than 24 hours after irradiation. The US Food and Drug Administration's stipulation for use of the Animal Rule led to standardization and in-depth characterization of models of acute radiation exposure and delayed radiation effects in critical organs (4). As a result of its systematic approach, the CMCR network has explored novel paradigms and identified and validated new targets. Unbiased high-throughput screening of chemical- or RNA-based libraries, as well as targeted exploration of defined agents and cells (5), has identified novel mitigators. For example, mitochondrion-targeted agents, such as the Gramicidin S (GS)-nitroxide JP4-039, effectively mitigate hematopoietic acute radiation syndrome (ARS) at >24 hours after radiation (6). Interestingly, many newly identified mitigators counter the proinflammatory effects of radiation, and the link between radiation-induced cytokines and the vascular system suggests possible avenues of research, including the autologous transfer of endothelial progenitor cells (7). Stromal bone marrow–derived cells also have been shown to mitigate against intestinal radiation damage (8). Although granulocyte colony-stimulating factor is currently the only US Food and Drug Administration–approved cytokine mitigator, others investigated through the CMCR, such as growth hormone, epidermal growth factor, and pleiotrophin, have been shown to mitigate hematopoietic ARS (9). Finally, work from the CMCR indicates that the various delayed effects of radiation injury are predicated on multiple downstream pathways, each of which may require mitigation as part of a targeted and multiagent approach (10). Critically, as approaches to the treatment of ARS improve early survival, mitigation of delayed effects will increase in importance.

Unfortunately, the ongoing unrest in the Middle East and around the globe suggests that terrorist threats have yet to be reduced. Increased investment, therefore, is required to meet the continuing and urgent need to develop and put in place appropriate dosimetric and therapeutic capabilities for dealing with a large-scale radiological or nuclear event. The development of radiation countermeasures should be made a priority, particularly because such agents may find dual utility as part of cancer-related radiation therapy. Given the current economic realities of shrinking budgets, it is clear that such an investment is critical to keep academic, industrial, and government scientists engaged in the effort to counter radiological threats to both civilian and military populations.

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