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Are We Ready for a Radiological Terrorist Attack Yet? Report from the CMCR Network

David J. Brenner, PhD¹, Nelson J. Chao, MD, MBA², Joel S. Greenberger, MD³, Chandan Guha, MD, PhD⁴, William H. McBride, PhD, DSc⁵, Harold M. Swartz, MD, PhD⁶, and Jacqueline P. Williams, PhD, FASTRO^{7,*}

¹Center for Radiological Research, Columbia University Medical Center, New York, NY 10032

²Department of Medicine, Duke University Medical Center, Durham, NC 27705

³Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA 15232

⁴Department of Radiation Oncology, Albert Einstein College of Medicine, New York, NY

⁵Department of Radiation Oncology, University of California Los Angeles, Los Angeles, CA 90095

⁶Department of Radiology, The Geisel School of Medicine at Dartmouth, Lebanon, NH 03766

⁷Department of Environmental Medicine, University of Rochester Medical Center, Rochester, NY 14642

The events of 9/11 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 ten years of funding, the CMCR leadership felt it appropriate to appraise the radiation community of its progress, particularly towards its two main goals: firstly, to develop after-the-fact dosimetry, and, secondly, 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, is able to

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*Corresponding author: Department of Environmental Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Box EHSC, Rochester, NY 14642. Tel.no.: (585) 275-1687, Fax no.: (585) 756-4966, jackie_williams@urmc.rochester.edu. .

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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 EPR 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 administered no earlier than 24 hours post-irradiation. The FDA'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), have identified novel mitigators. For example, mitochondrion-targeted agents, such as the GS-nitroxide, JP4-039, effectively mitigate hematopoietic ARS at >24 hours post-radiation (6). Interestingly, many newly identified mitigators counter the pro-inflammatory 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 G-CSF is currently the only FDA-approved cytokine mitigator, others investigated through the CMCR, such as growth hormone, EGF, and pleiotrophin, have been shown to mitigate hematopoietic ARS (9). Finally, work from the CMCRs 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 multi-agent 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 since 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 in order 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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