HHS Public Access

Author manuscript

*Radiat Res*. Author manuscript; available in PMC 2021 August 25.

Published in final edited form as:

*Radiat Res*. 2018 April ; 189(4): 446. doi:10.1667/RR5LTE.1.

# Response to the 'Comments on "Cellular Therapies for Treatment of Radiation Injury after a Mass Casualty Incident" (Radiat Res 2017; 188:242-45)' by Drouet *et al*. (Letters to the Editor, Radiat Res 2017; 188:463)

**R. Tamarat**[a], **M. Benderitter**[a], **J. R. Jourdain**[a], **B. W. Maidment**[b], **F. Macchiarini**[c], **C. I. Rios**[d], **A. L. DiCarlo**[d]

[a]Institute of Radioprotection and Nuclear Safety (IRSN), Fontenay-aux-Roses, France

[b]Previously - RNCP, DAIT, NIAID, NIH, Rockville, Maryland

[c]Previously - RNCP, DAIT, NIAID, NIH; now National Institute on Aging (NIA), NIH, Bethesda, Maryland

[d]Radiation and Nuclear Countermeasures Program (RNCP), Division of Allergy, Immunology and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Rockville, Maryland

We deeply appreciate the comments from Drouet and colleagues regarding our recent report on "Cellular Therapies for Treatment of Radiation Injury: Report from a NIH/NIAID and IRSN Workshop" published in Radiation Research by DiCarlo *et al*. (1). We would like to point out that Drouet and colleagues reference two separate publications that resulted from the meeting - the commentary titled "Cellular Therapies for Treatment of Radiation Injury after a Mass Casualty Incident" by Rios *et al*. (2); and our full meeting report "Cellular Therapies for Treatment of Radiation Injury: Report from a NIH/NIAID and IRSN Workshop" by Di Carlo *et al*. (1). For clarity, we will address exclusively the points Drouet *et al*. raised regarding the full meeting report.

1. In their editorial, the authors discussed the low efficiency of unmatched MSC obtained from banking in case of mass casualty, referring to their own study (3). Decades of robust research in the stem cell community have established that administration of frozen therapeutic cells is less effective than use of fresh cells. As highlighted and largely discussed by Dr. J. Galipeau in the full Cellular Therapies Meeting Report, it has been clearly demonstrated that, before injection, thawed cells need to be cultured, to activate their metabolism and enhance their efficacy. It is clear that the lack of therapeutic potential of the MSC-approach reported by Riccobono *et al*. (3) was due to the use of cells that had been previously cryopreserved. In fact, in our view, the main finding of that study was not the predictable lack of efficiency of the cryopreserved allogenic cells, but rather, the unexpected beneficial effect achieved after administration of frozen autologous cells. It would therefore be helpful to know the details of their study's experimental protocol.

**2.** The authors mentioned that “Studies are currently being performed to explore derived strategies such as culture cell media use and micro vesicles injection, but it is yet unclear whether these approaches would present any therapeutic efficacy *in vivo* in the context of radiation-induced injuries.” To address this concern, several studies have demonstrated the therapeutic efficacy of exosomes derived from different cell types (MSCs, ECs, adipose-derived progenitor cells) in multiple pathological animal models, including kidney, heart and lung (4). More importantly, several clinical trials aimed at using exosomes as therapeutic tools or vehicle for drug delivery have also been published (5). For example, exosomes purified from dendritic cells pulsed with antigenic peptides were used as anticancer vaccines against melanoma and non-small cell lung cancer (NSCLC) in two Phase I clinical trials (*6, 7*), and more recently, against NSCLC in a Phase II clinical trial (7). Allogeneic MSC-derived exosomes may also harbor unchallenged immunosuppressive potential as suggested by a case study in which their administration mitigated the symptoms and pathology of graft-vs.-host disease (8). Furthermore, unpublished data from the IRSN have demonstrated the beneficial effect of exosomes in the healing of radiation-induced skin lesions, as well as in the mitigation of gastrointestinal syndrome in experimental animal models (with financial support from the French National Research Agency and the U.S. National Institutes of Health). Finally, as mentioned in the meeting report, Dr. C. Limoli’s team recently published a study demonstrating the beneficial therapeutic effect of stem cell-derived microvesicles *in vivo*, in the context of radiation-induced brain injury (9). Altogether, these results suggest that extracellular membrane vesicle-based strategies could be a useful and efficient therapeutic approach in the context of radiation-induced injuries.

## REFERENCES

1. DiCarlo AL, Tamarat R, Rios CI, Benderitter M, Czarniecki CW, Allio TC, Macchiarini F, Maidment BW, Jourdain JR. Cellular therapies for treatment of radiation injury: report from a NIH/NIAID and IRSN workshop. Radiat Res2017; 188:e54–75. (online only) [PubMed: 28605260]
2. Rios C, Jourdain JR, DiCarlo AL. Cellular Therapies for Treatment of Radiation Injury after a Mass Casualty Incident. Radiat Res2017; 188:242–45. [PubMed: 28609636]
3. Riccobono D, Agay D, Scherthan H, Forcheron F, Vivier M, Ballester B, Meineke V, Drouet M. Application of adipocyte-derived stem cells in treatment of cutaneous radiation syndrome. Health Phys2012; 103:120–6. [PubMed: 22951469]
4. Flamant S, Tamarat R. Extracellular vesicles and vascular injury: new insights for radiation exposure. Radiat Res2016; 186:203–18. [PubMed: 27459703]
5. Ohno S, Drummen GP, Kuroda M. Focus on extracellular vesicles: development of extracellular vesicle-based therapeutic systems. Int J Mol Sci2016; 17:172. [PubMed: 26861303]
6. Escudier B, Dorval T, Chaput N, Andre F, Caby MP, Novault S, et al.Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of the first phase I clinical trial. J Transl Med2005; 3:10. [PubMed: 15740633]
7. Morse MA, Garst J, Osada T, Khan S, Hobeika A, Clay TM, et al.A phase I study of exosome immunotherapy in patients with advanced non-small cell lung cancer. J Transl Med2005; 3:9. [PubMed: 15723705]

8. Kordelas L, Rebmann V, Ludwig AK, Radtke S, Ruesing J, Doeppner TR, et al.MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. Leukemia2014. (https://www.nature.com/articles/leu201441)

9. Baulch JE, Acharya MM, Allen BD, Ru N, Chmielewski NN, Martirosian V, et al.Cranial grafting of stem cell-derived microvesicles improves cognition and reduces neuropathology in the irradiated brain. Proc Natl Acad Sci U S A2016; 113:4836–41. [PubMed: 27044087]