"Radiation Oncology. Optimal Health for all, Together": a CRISPR step away?

In October 2020, Professor Emmanuelle Charpentier and Professor Jennifer Doudna were awarded the Chemistry Nobel Prize. Their discovery? DNA sequences called clustered regularly interspaced short palindromic repeats, or CRISPR - an acronym that has become common language in the scientific community around the globe. Discovered just eight years ago,1 these genetic scissors represent the most disruptive technology since the polymerase chain reaction (PCR).[2]

Bacteria and archaea use CRISPR and CRISPR-associated (Cas) systems to fight attacks from viruses and plasmids and to protect themselves from invasion.[3] This form of adaptive immunity involves the sequence-specific detection and silencing of foreign nucleic acids. Professor Charpentier and Professor Doudna transformed this capacity into a powerful gene editing tool. While CRISPR-Cas9 is rapidly revolutionising life sciences, one question is: will it turn radiobiology upside down too?

The original goal of CRISPR-Cas9 was to enable gene editing and the eradication of disease. This tool has since generated many new models of disease.[4] By controlling the expression of specific genes, the technology is transforming our ability to study the effects of radiation. The development of patient-derived organoids is a successful example of the application of CRISPR technology in order to model diseased and healthy tissues. [5] These models are elegant supporters of the study of stem-cell responses to radiation,[6,7] but their genetic manipulation with CRISPR can push their capabilities further. Genetically edited organoid models of meningioma helped in the identification of *CDH2* and *PTPRZ1* as potential new gene targets for meningioma therapy. This experimental model in turn was used to link the presence of a pre-operative region of interest with a high apparent diffusion coefficient value on MRI to the existence of meningioma regions that contained proliferating cells that were enriched for developmental gene expression programmes.[8]

One key possible transformative contribution of the Charpentier-Doubna discovery might be the exciting opportunity to study the DNA damage response. CRISPR-based technologies are enabling genome-wise screens of gene function in mammalian cells, which are assisting in the identification of novel therapeutic targets and drug-gene interactions for improved radio sensitisation of tumours.[9-11] Furthermore, CRISPR screens could facilitate the molecular stratification of patients. Loss of function screening of DNA damage-response processes has been found to identify differences in the contribution of these processes to radiotherapy response between human papilloma virus (HPV)-positive and HPV-negative head-and-neck squamous cell carcinomas.[12] But more than this, CRISPR may have a transformative impact in radiobiology due to its ability to artificially generate radiation-like DNA-damage clusters that are representative of different cumulative doses, linear energy transfer (LET) and possibly dose rates. This capacity could answer critical outstanding questions on the contribution of DNA damage amount, complexity, and competitive repair path to the desired impact on cell proliferation, including non-targeted effects.[13] The anticipation is that the CRISPR/Cas9 method could be used to dissect the mechanistic biochemical basis of the relationship between the induction of DNA double-strand breaks, and their repair and cellular responses. Already, the development of CRISPR-based assay systems to measure DNA double-strand-break repair are enabling the study of the competitiveness of DNA-repair pathways, and are advancing our understanding of chemo-radiation interactions.[14,15]

This month marks the 125th anniversary of the discovery of X-rays by Wilhelm Röntgen. This was a discovery that sparked the beginning of the wonderful story of our field, and its clinical revolution. The efficacy of radiation therapy can be further improved, and efforts to improve its accessibility to the one-in-four cancer patients who require but are not offered this treatment are expected to save many lives.[16] Professor Charpentier and Professor Doubna undoubtedly did not anticipate that their discovery eight years ago could help to address these challenges. But watch this space – CRISPR might turn our field upside down in ways that we have yet to witness.

Dr Laure Marignol
Associate professor, radiobiology
Discipline of Radiation Therapy
Trinity College Dublin
Dublin, Ireland
marignl@tcd.ie

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