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Activation of novel prodrugs by X-rays and gamma rays - towards combined chemo- and radiotherapy with little side effects

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Combined external beam radiotherapy and chemotherapy are known to have much more favourable disease outcome due to synergistic working, e.g., DNA repair inhibition by drugs making ionizing radiation more potent. However, anti-tumour drugs are known to cause severe adverse effects since they attack healthy fast dividing cells besides cancer cells. To minimize the systemic toxicity of such chemotherapeutics, we designed a prodrug (also called caged drug), which becomes active only upon removal of a protecting group, triggered by external ionizing radiation. Using such a strategy, the drug toxicity to healthy tissue is greatly reduce, while still achieving high killing efficiency to tumour cells. To proof this concept, a fluorescent probe, 4-methyl-7-hydroxycoumarin, was used as the reporter instead of the drug, to enable easy evaluation of the working mechanism. The hydroxy group of the probe was protected by an aryl boronate ester based self-immolative linker through a carbonate bond, and thus the fluorescence is largely quenched because of the electron withdrawing property of the latter. The aryl boronate ester can be oxidised by hydrogen peroxide which is generated by the radiolysis of water, leading to the release of the reporter (the fluorescent probe). When this compound was irradiated by X-ray or gamma radiation, a significant increase of the emission intensity was observed, which demonstrates that the protecting group was successfully removed. More importantly, an increase of fluorescence emission intensity is already detected when the probe solution is exposed to just 2 Gy of radiation, which is typically used in external beam therapy. After confirming the release of the reporter triggered by ionizing radiation, we replace the fluorescent probe by a widely used anti-tumour drug, doxorubicin. The toxicity of this prodrug appeared to be 10 times less than free drug, and the release of doxorubicin after irradiation was successfully detected by liquid chromatography –mass spectrometry (LC-MS). Currently we are conducting cell experiments to test the killing efficiency of this prodrug when exposed to ionizing radiation and determine its potential in combined chemo- and radiotherapy.

Primary authors: DENKOVA, Antonia (TU Delft); LIU, Juncheng (Delft University of Technology); EELKEMA, Rienk (TU Delft)

Presenter: LIU, Juncheng (Delft University of Technology)

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