*Prayogik Rasayan*

# X-ray Triggered Activation of Doxorubicin Prodrugs for Concurrent Chemo-Radiotherapy: A Review

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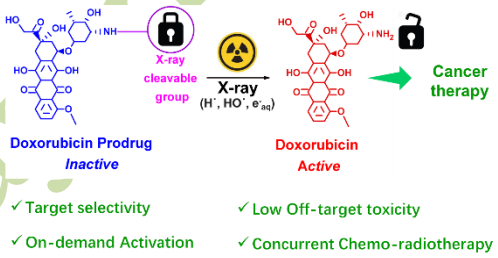
## Abstract

Doxorubicin (DOX), a potent chemotherapeutic drug, suffers from severe cardiotoxicity and severe off-target side effects that constrain its therapeutic index. This review depicts the emerging paradigm of X-ray activatable DOX prodrugs, which harness clinically relevant ionizing radiation as an external trigger to achieve spatiotemporal control over drug release, thereby enabling precision Concurrent chemo-radiotherapy (CRT) which represents a frontier in cancer management. Herein, we systematically reviewed the key design strategies focusing on radiosensitive linkers/moieties, mechanistic pathway underlying X-ray-induced cleavage for prodrug activation within the tumor microenvironment to provide a blueprint for future development and inspire researchers to explore DOX prodrugs with real clinical applications.




***Keywords:*** *Radiotherapy, Doxorubicin prodrug, Concurrent Chemo-radiotherapy, Cancer treatment*

## 1. Introduction

Cancer remains one of the leading causes of mortality worldwide, with an estimated 20 million new cases and 10 million deaths annually, underscoring the urgent clinical need for more effective and less toxic therapeutic modalities.[1] Among the arsenal of FDA approved chemo-therapeutic drugs, doxorubicin (DOX), an anthracycline antibiotic, has been administered to treat several kinds of cancers spanning blood cancer, acute lymphoblastic leukemia, acute myeloblastic leukemia, and Hodgkin and non-Hodgkin lymphoma during chemotherapy for over last four decades due to its potential antitumor activity which from intercalation with DNA, inhibition of topoisomerase II, and generation of reactive oxygen species (ROS), culminating in apoptosis. Despite of its clinical efficacy against a wide range of solid tumors and hematological cancers, DOX administration is severely hampered by dose-dependent, cumulative cardiotoxicity, which often leads to irreversible cardiomyopathy and congestive heart failure. This noted side effects, coupled with off-target toxicities on healthy tissues and rapid plasma clearance, urges the development of targeted delivery that can improve its therapeutic index while preserving efficacy.[2,3,4]

Concurrent chemo-radiotherapy (CRT) has emerged as a standard-of-care for numerous cancers, leveraging the synergistic interaction between radiotherapy (RT) and chemotherapy. However, conventional CRT suffers from significant limitations which includes (i) systemic administration of chemotherapeutics are often exposes non-targeted organs, (ii) inefficient drug accumulation to hypoxic tumors, and (iii) temporal discordance between drug pharmacokinetics and radiation fractions reduces therapeutic synchronization. These challenges demand innovative strategies that enable spatially confined, temporally controlled drug activation precisely within the irradiated tumor volume.[5]

The prodrug approach offers a compelling solution by rendering chemotherapeutics pharmacological inertness until activation at the target site. While numerous tumor-specific triggers have been explored including pH, enzymes, hypoxia, ultrasound, light etc all of which often lack the precision, spaciotemporal controllability, penetration depth for real clinical translatability required for deep-seated tumors.[6,7]

X-ray irradiation, a ubiquitous tool in clinical oncology, presents a unique external trigger that combines deep tissue penetration (up to any depth) with exceptional spatiotemporal precision. X-ray activatable prodrugs are designed to remain stable during systemic circulation in vivo and undergo selective activation exclusively within the radiation field, thereby achieving on-demand chemotherapeutic drug release synchronized with radiotherapy (RT) fractions. Thus, Radiotherapy induced prodrugs activation hold transformative clinical potential to redefine CRT by merging radiation therapy with on-demand chemotherapy, offering a blueprint for next-generation combination therapies to treat cancer.[8]

Radiotherapy induced prodrugs activation hold transformative clinical potential to redefine CRT by merging radiation therapy with on-demand chemotherapy, offering a blueprint for next-generation combination therapies to treat cancer. This paradigm not only minimizes systemic exposure and off-target toxicity but also concentrates therapeutic payload within the tumor microenvironment (TME), potentially overcoming hypoxia-associated resistance. The mechanistic pathways of X-ray-induced activation is multifaceted which may be triggered by: (i) Direct radiolysis involving cleavage of chemical bonds by high-energy photons or secondary electrons, particularly targeting fragile linkers such as dichalcogenide bonds (S-S, Se-Se, Te-Te), C–O, N–O,

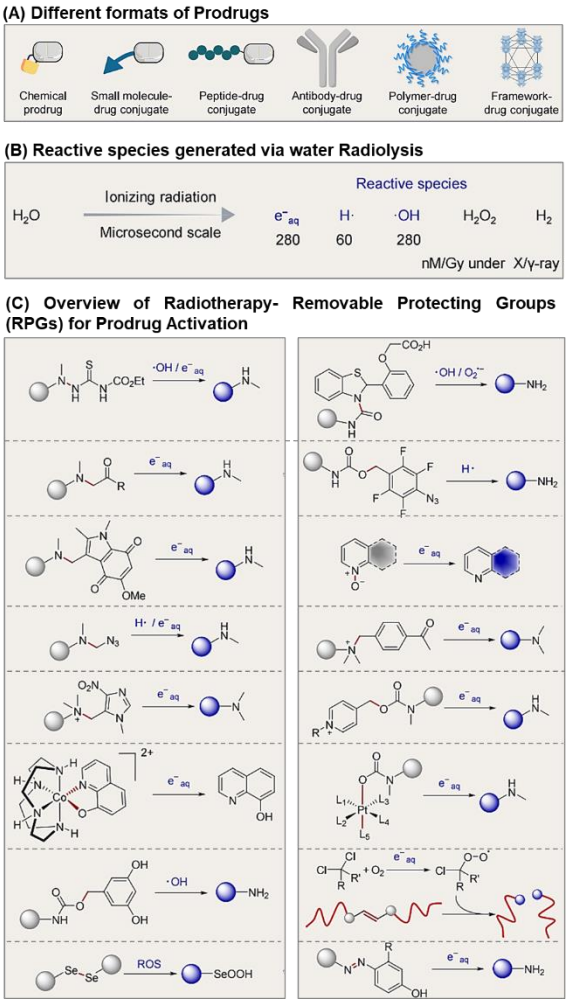



**Figure 1**. (a) Various forms of prodrugs which have been reported or are waiting to be developed.; (b) The reactive species generated by the radiolysis of water under ionizing radiation like X-ray or g-rays. The radiolytic yields of reactive species generated are given beneath with numbers. The unit "Gy" refers to the absorbed X-raydose, which is defined as joule per kilogram (J/Kg) of substance.; (c) Overview of the Radiotherapy-Removable Protecting Groups (RPGs) for Prodrug Activation. Adapted with permission from Reference *** Copyright 2025 American Chemical Society

quaternary Nitrogen bonds, nitroaryl groups, or photocaged quinone motifs**********, (ii) scintillator-mediated energy transduction employs nanomaterials (e.g., lanthanide-doped nanoparticles, perovskite quantum dots, or organic phosphors) that absorb X-rays and emit UV/visible light, triggering removal of photolabile protecting groups, (iii) Radiation-generated ROS, including hydroxyl radicals (•OH) and superoxide anions also facilitate linker cleavage through oxidative or reductive pathways. Its worth to mention that depth-dependent X-ray attenuation and heterogeneous TME composition further complicate uniform activation. Additionally, the lack of standardized dosimetry protocols, scalable manufacturing under Good Manufacturing Practice (GMP), and comprehensive toxicity profiles of nanomaterials impede clinical translations.[9,10,11,12,13,14,15,16]

This review provides a comprehensive analysis of X-ray activatable DOX prodrugs, focusing their design principles, activation mechanisms, nanocarrier integration, and preclinical validation. Furthermore, we have addressed existing challenges and outlined future directions. By consolidating recent progress and identifying critical gaps, this review aims to catalyze the translation of X-ray responsive doxorubicin prodrugs into clinically viable CRT regimens, ultimately redefining the therapeutic landscape for cancer patients.

## 2. Result and discussion:

### 2.1 Activation of tetrafluoroaryl azide -Azide based Doxorubicin Prodrug

Geng et. al demonstrated radiotherapy triggered cancer prodrugs activation using clinically relevant doses of X-ray irradiation, enabling simultaneous radiotherapy and site-directed chemotherapy which differs from conventional chemo-radiotherapy (which uses drugs to sensitize tumors to radiation) by physically converting inactive prodrugs into active chemotherapeutics directly at the tumor site.[17] Using high-throughput screening the researchers identified sulfonyl azides and tetrafluoroaryl azides as functional groups that undergo radiation-induced reduction to amines via free radical chemistry ($HO^{\cdot}$, $H^{\cdot}$ generated by ionizing radiation). This reaction occurs efficiently even in hypoxic conditions mimicking tumor microenvironments. As a Proof-of-Concept they demonstrated activation of 7-azido-4-methylcoumarin (non-fluorescent probe) to its fluorescent amine form with >90% efficiency at 60 Gy X-ray dose, showing successful activation in HeLa cells. They also demonstrated activation of a sulfonyl azide-caged prodrug of pazopanib (VEGF inhibitor) which achieved >90% conversion to active drug at 24 Gy. In vitro, irradiated prodrug showed equivalent cytotoxicity to free pazopanib against endothelial cells.

Finally, a tetrafluoroaryl azide-caged doxorubicin prodrug underwent two-step activation (azide reduction + 1,6-self-immolation followed by decarboxylation) with 50% conversion at 60 Gy. The prodrug was non-toxic alone but became highly cytotoxic after irradiation. In HT29 tumor-bearing mice, combination treatment (prodrug + 6 Gy radiation) matched the efficacy of free drug showing dramatic tumor growth inhibition and prolonged survival with improved tolerability and significantly reduced doxorubicin's cardiotoxicity, as evidenced by lower plasma levels of cardiac damage markers (CK, CK-MB, LDH).

Key Advantages of this study demonstrated: (i) **Spatial control**: Drug activation only occurs where radiation is applied, minimizing systemic toxicity.; (ii) **Temporal control**: Real-time drug release during radiotherapy sessions.; (iii) **Stability**: Prodrugs remain intact in blood and biological fluids during circulation.; (iv) **Reduced side effects**: Maintains therapeutic efficacy while decreasing off-target organ damage.

This approach established "*ionizing irradiation-mediated chemistry*" as a new paradigm for targeted chemotherapy combined with radiotherapy with improved therapeutic indices. (Figure 2)

through clinical X-ray irradiation, thereby addressing the persistent challenge of off-target toxicity in targeted cancer therapies.[18]

The molecular designing comprises three core components: a therapeutic payload (e.g Doxorubicin), a radiation-responsive 3,5-dimethyloxybenzyl alcohol (DMBA) caging

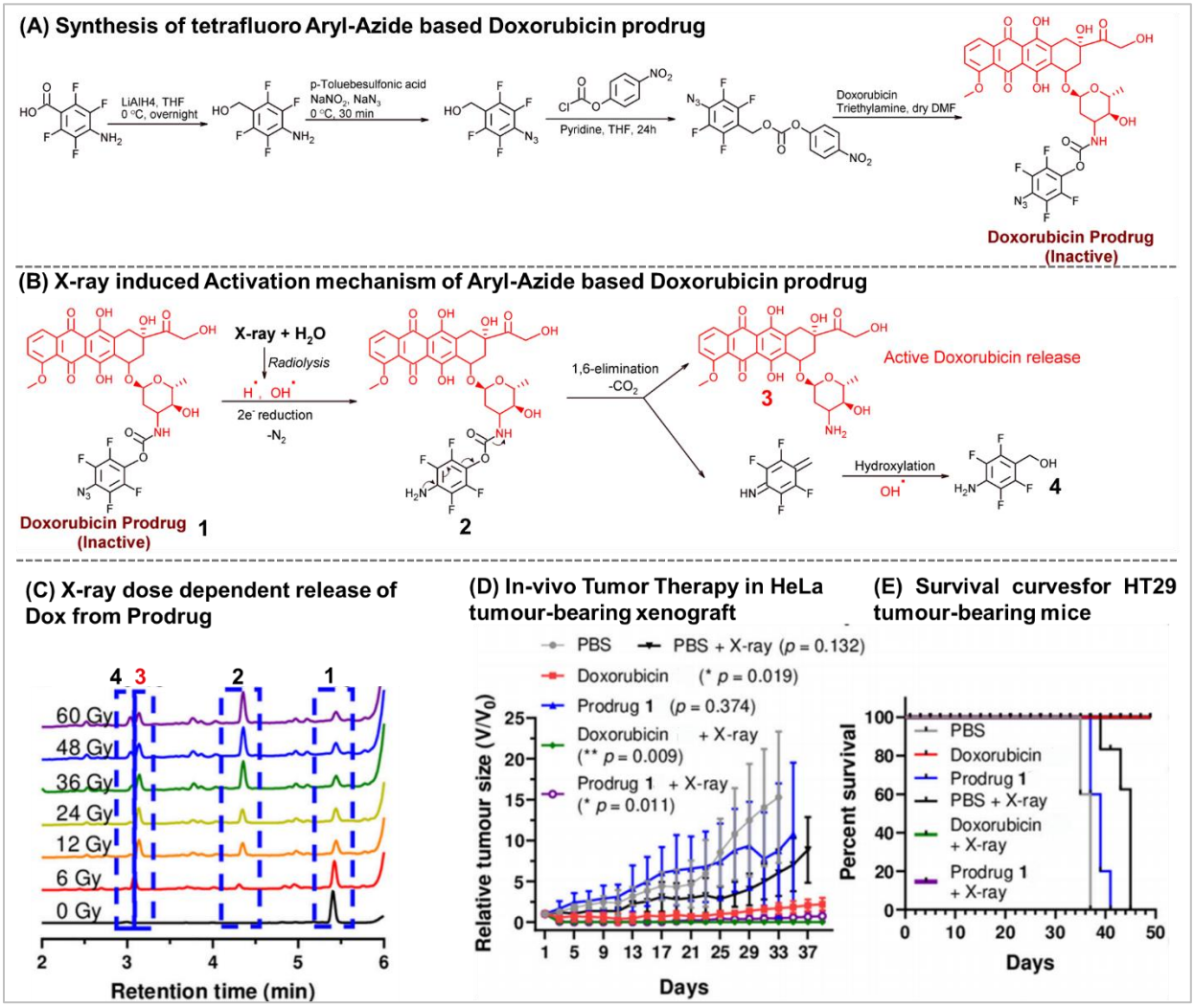



**Figure 2**. (a) Synthesis scheme of X-ray activable tetrafluoro-aryl-Azide -linked Doxorubicin prodrug.; (b) mechanistic pathway for liberation of doxorubicin.; (c) HPLC traces of the reaction mixture of Dox-prodrug **1** after irradiation with 0 Gy to 60 Gy, showing unreacted prodrug prodrug **1** ($R_T$ = 5.40 min), intermediate **2** ($R_T$ = 4.36 min), doxorubicin **3** ($R_T$ = 3.14 min) and **4** ($R_T$ = 3.03 min).; (d) In vivo studies in HeLa tumor bearing BALB/c nude mice with prodrug **1** by intra-tumoral injection. 4 h post injections, mice were treated with or without 6 Gy of X-ray irradiation. Tumor burdens were measured every other day using a caliper. The data are presented as mean ± SD (n = 5). Statistical analysis was performed using one-way ANOVA with Dunnett post-test compared to PBS treated mice at day 33.; (e) Survival curves for HT29 tumor bearing mice. Mice were aged until moribund or the tumor volume reached 2000mm$^3$. (n = 5). The data are presented as mean ± SD (n = 5). Statistical analysis was performed using one-way ANOVA with Dunnett post-test compared to PBS treated mice at day 33. Adapted with permission from reference **17** Copyright 2021 @ Nature Chemistry

moiety, and a self-immolative linker (SIL) with a maleimide anchor for robust thiol-based conjugation to delivery vehicles such as serum albumin or antibodies.

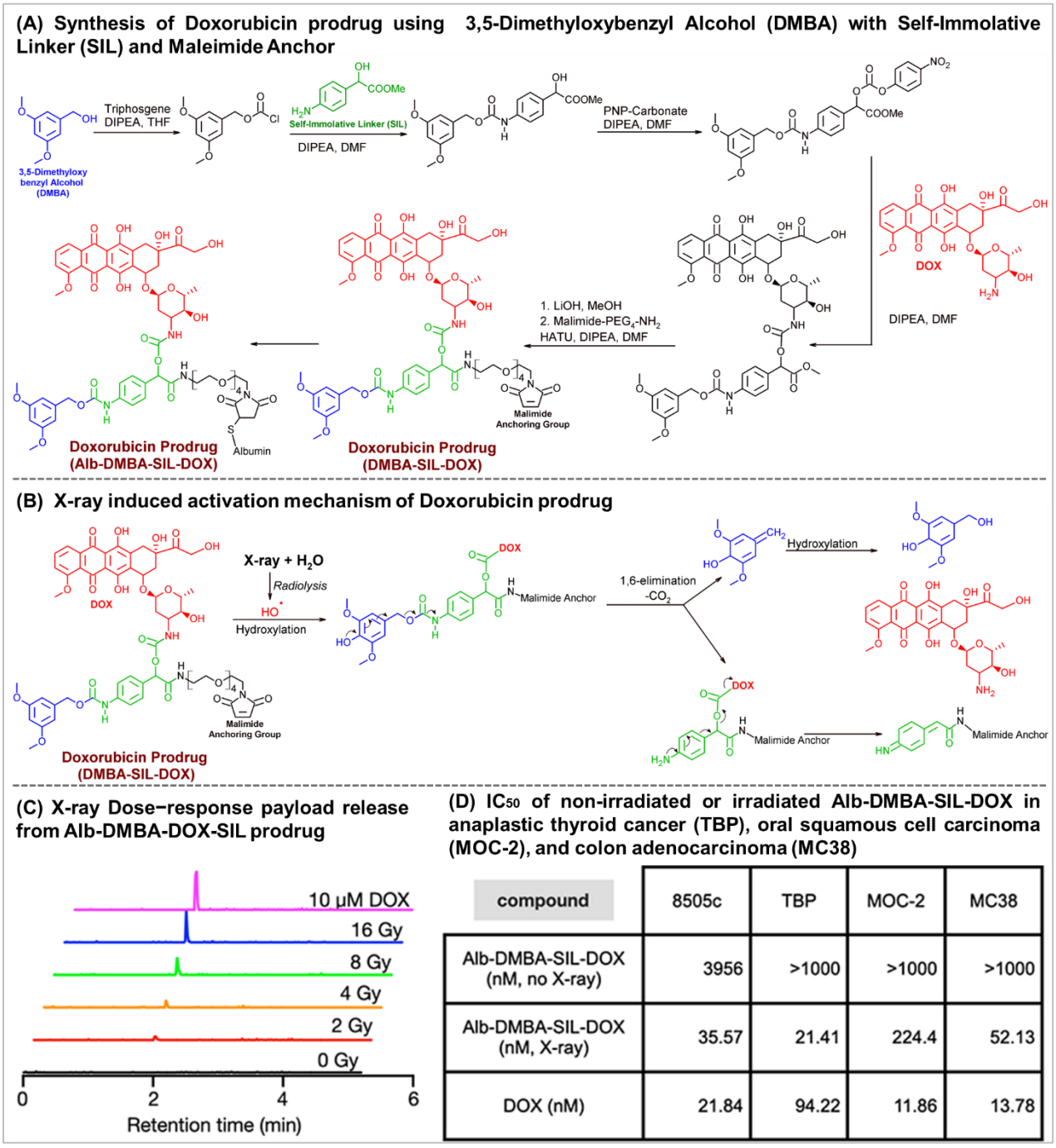
### 2.1.2 Activation of DMBA Self-immolative linker-based Doxorubicin Prodrug

Miller et. al developed an innovative X-ray radiation-cleavable drug-conjugate linker system that enables spatially localized activation of potent cytotoxic payloads

The mechanism of activation relies on ionizing radiation-generated hydroxyl radicals that hydroxylate the DMBA benzyl ring, initiating a cascade of 1,4- and 1,6-elimination reactions followed by decarboxylation that spontaneously decage the active drug with approximately 50-70% efficiency at a clinically relevant single dose of 8 Gy,

compatible with hypo fractionated radiotherapy protocols. Notably, this radiation-activated release is paradoxically enhanced under hypoxic conditions (0.005 atm $pO_2$), making it particularly suitable for targeting radioresistant hypoxic tumor microenvironments that typically limit radiotherapy efficacy.

In vitro experiments with/without X-ray irradiation across




| compound | 8505c | TBP | MOC-2 | MC38 |
|---|---|---|---|---|
| Alb-DMBA-SIL-DOX (nM, no X-ray) | 3956 | >1000 | >1000 | >1000 |
| Alb-DMBA-SIL-DOX (nM, X-ray) | 35.57 | 21.41 | 224.4 | 52.13 |
| DOX (nM) | 21.84 | 94.22 | 11.86 | 13.78 |

**Figure 3**. (a) Synthesis of 3,5-Dimethyloxybenzyl Alcohol (DMBA) Prodrugs with Self-Immolative Linker (SIL) and Maleimide Anchor.; (b) Drug release initiation via radical hydroxylation under hypoxia followed by 1,6-elimination and subsequent loss of the SIL caging group and consequent releases the caged drug payload.; (c) LC-MS chromatographs of DOX (isolated mass of 544.4) released from Alb-DMBA-SIL-DOX prodrug.; (d) Half-maximal inhibitory concentration ($IC_{50}$) of non-irradiated or irradiated Alb-DMBA-SIL-DOX in cancer cell lines of anaplastic thyroid cancer (TBP), oral squamous cell carcinoma (MOC-2), and colon adenocarcinoma (MC38). Adapted with permission from reference **18**. Copyright 2022 @American Chemical Society.

multiple aggressive cancer cell lines including anaplastic thyroid cancer (8505c, TBP), colon adenocarcinoma (MC38),

pancreatic adenocarcinoma (iKRAS) and oral squamous cell carcinoma (MOC-2) using the albumin-conjugated

doxorubicin prodrugs (Alb-DMBA-SIL-DOX) demonstrated excellent reduction in $IC_{50}$ values after X-ray irradiation

restoring lethal potency to the levels of the parent drug. Mechanistic confirmation employed sophisticated live-cell

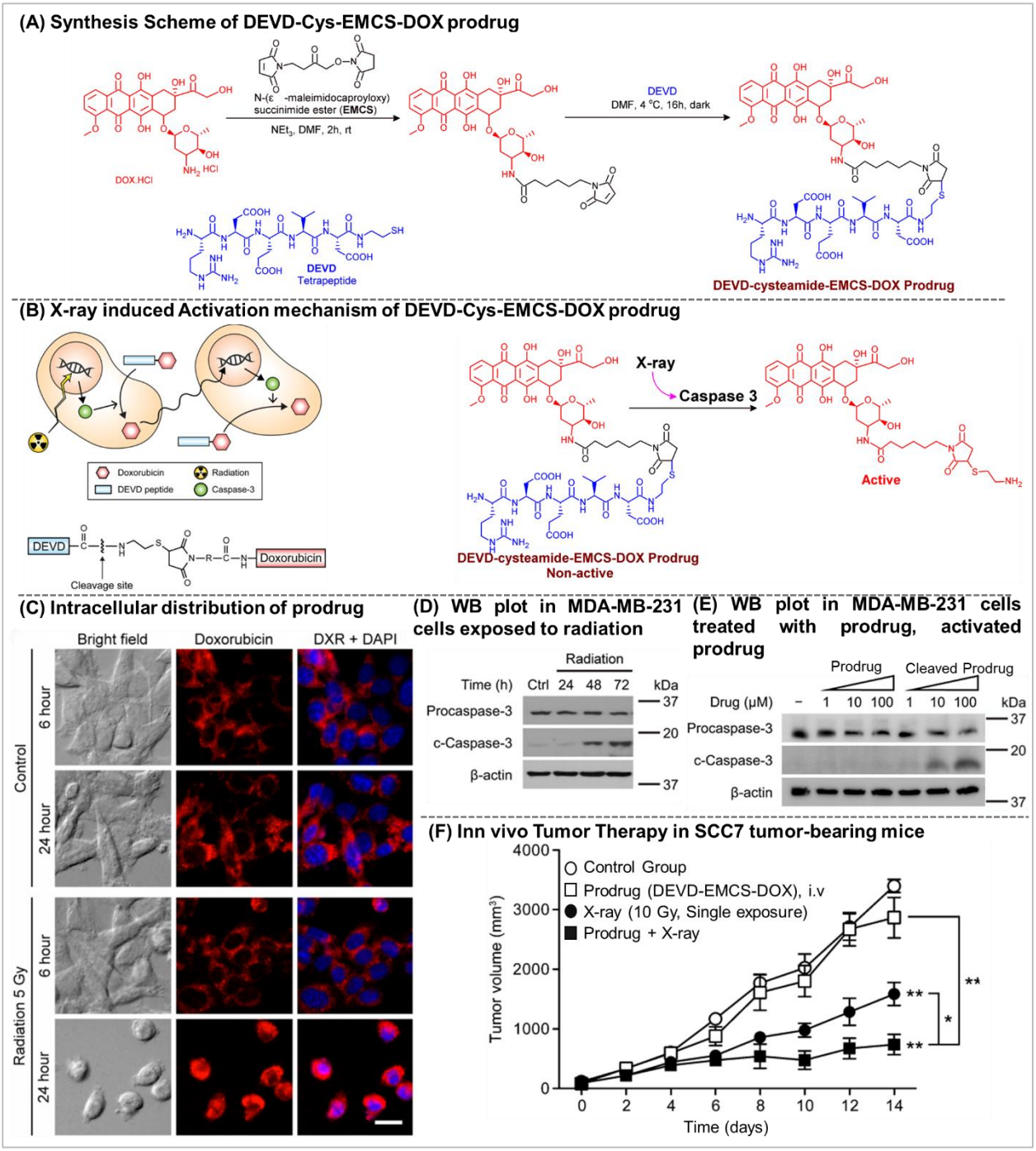



**Figure 4**. (a) Synthesis of Maleimide Derivatives of Doxorubicin via Amide Linkage and corresponding synthesis of DEVD-EMCS-DOX prodrug.; (b) Schematic illustration of the caspase-3-mediated apoptosis targeted doxorubicin prodrug system and representative structure of the prodrug and the site of cleavage bycaspase-3.; (c) Intracellular distribution of DEVD-EMCS-DOX prodrug with or without radiation treatment on MDA-MB-231 cells. Red and blue fluorescence represent the doxorubicin moiety and the nucleus, respectively. Scale bar, 100 μm.; (d) Western blot of procaspase-3 (35 kDa) and cleaved caspase-3 (c-Caspase-3; 17kDa) of MDA-MB-231 cells exposed to radiation.; (e) the cells treated with prodrug, activated prodrug (prodrug 13 preincubated with commercially available caspase-3).; (f) Tumor growth inhibition studies on SCC7 tumor-bearing mice. Control (○), prodrug (□; 5 mg/kg; daily i.v. administration for 7 days), radiation 10 Gy only (●) single exposure, and combination of prodrug + radiation (■, identical dose and dosing schedule as described above). Data are expressed as the means ± SEM. *P < 0.05, **P < 0.005 versus the control or as specified. Adapted with permission from reference **19**. Copyright 2015 @American Chemical Society

imaging: an EB3-mApple microtubule reporter system revealed that non-irradiated conjugates had no effect on

microtubule dynamics, whereas radiation-activated MMAE fully abrogated microtubule polymerization; similarly, doxorubicin conjugates remained confined in cytoplasm until irradiation enabled nuclear accumulation and DNA intercalation, as visualized by intrinsic fluorescence.

The versatility of the platform was further demonstrated through successful translation to antibody-drug conjugates (ADCs) using anti-EGFR monoclonal antibodies, achieving comparable results with 64-70% drug release, 70-fold cytotoxicity enhancement post-irradiation, and similar nuclear targeting profiles. This strategy also established a clinically translatable paradigm for achieving unprecedented spatiotemporal control over drug activation, particularly for hypoxic tumors that require synergistic combination therapeutics. (Figure 3)

### 2.1.3 Activation of DEVD-Peptide conjugated Doxorubicin Prodrug

Youngro et. al developed and optimized a radiation-induced apoptosis triggered caspase-3-activatable doxorubicin prodrug to overcome the limitations of active tumor targeting, thereby circumventing the pitfalls of tumor heterogeneity and systemic toxicity associated with conventional chemotherapy.[19] Recognizing that intra-tumoral genomic heterogeneity compromises ligand-based targeting strategies, the researchers exploited radiation-induced apoptosis as a universal trigger, wherein ionizing radiation upregulates caspase-3 expression to locally activate a DEVD peptide-conjugated doxorubicin prodrug.

The prodrug designing involved linking doxorubicin to a DEVD tetrapeptide via a heterobifunctional maleimide-NHS ester linker, where the DEVD moiety served as a caspase-3 substrate while also sterically hindering nuclear entry of the inactive prodrug. Through systematic evaluation of multiple heterobifunctional linkers (SMCC, EMCS, MBS, SMPB, AMAS) and thiol-bearing residues (e.g cysteine vs. cysteamine), the researchers determined that cysteamine lacking a carboxylic acid group was essential, as the negative charge in cysteine derivatives electrostatically repelled DNA and prevented nuclear accumulation. Among the linkers tested, the EMCS (N-(ε-maleimidocaproyloxy) succinimide ester) linker provided optimal flexibility and length with the most potent active metabolite ($IC_{50}$ = 4.6 μM) with efficient nuclear localization, while shorter or more rigid linkers suffered from steric hindrance that limited activity. Thus, the final prodrug was synthesized by conjugating doxorubicin-cysteamine-EMCS to DEVD peptide, which demonstrated exceptional caspase-3 specificity, achieving >98% cleavage to release active doxorubicin in vitro, with no spontaneous degradation.

The activation mechanism initiates when ionizing radiation upregulates caspase-3 expression in apoptotic tumor cells; this cysteine protease specifically recognizes and cleaves the DEVD tetrapeptide sequence (Asp-Glu-Val-Asp) at the P1′ aspartic acid residue, liberating the active metabolite compound 8 (doxorubicin-cysteamide-EMCS) from the bulky, negatively-charged DEVD peptide moiety. Confocal microscopy confirmed that intact prodrug remained cytoplasmic due to the DEVD motif's three carboxyl groups and increased molecular weight, whereas caspase-3 cleavage enabled nuclear accumulation of the active drug.

In vitro studies with MDA-MB-231 breast cancer cells revealed that prodrug alone was essentially inactive up to 10 μM, but showed synergistic cytotoxicity when combined with 5 Gy radiation, reducing cell viability by 75% at 48 hours compared to 60% with radiation alone, coinciding with time-dependent caspase-3 upregulation and nuclear drug accumulation. In vivo evaluation in SCC7 tumor-bearing mice demonstrated that daily IV administration of prodrug (14 mg/kg, equivalent to 5 mg/kg doxorubicin) combined with a single 10 Gy radiation dose suppressed tumor growth by 79% vs. 53% with radiation alone, while prodrug monotherapy showed no significant effect. Critically, the prodrug exhibited substantially reduced systemic toxicity, as all treated mice maintained stable body weight, whereas free doxorubicin at equivalent doses caused 100% lethality within six days. This approach establishes a feedback amplification loop wherein radiation-induced apoptosis activates caspase-3 to cleave the prodrug, and the released active drug further activates caspase-3 in neighboring cells, overcoming tumor heterogeneity by targeting a conserved apoptotic pathway rather than specific tumor antigens, while the simple, high-yield chemistry and enhanced stability make it a promising candidate for clinical translation in localized tumors treatable with radiotherapy. (Figure 4)

## 3. Conclusions, Challenges and Future Prospects

The convergence of prodrug activation strategy with clinical radiotherapy has ushered in a transformative paradigm for precision cancer treatment, wherein X-ray irradiation serves as an external, spatially-selective trigger to activate doxorubicin payloads specifically within tumor volumes. Herein, we have reviewed the radiotherapeutic X-ray induced doxorubicin activation comprising tetrafluoroaryl azide reduction, DMBA self-immolative linker cleavage, and DEVD-peptide caspase-3 activation which collectively demonstrate that clinically relevant X-ray radiation (5–60 Gy) can efficiently trigger active Doxorubicin release while maintaining exquisite in vivo stability during systemic circulation.

These approaches achieve unprecedented spatiotemporal control, overcoming the fundamental limitations of conventional concurrent chemo-radiotherapy by eliminating systemic exposure, reducing off-target cardiotoxicity, and potentially circumventing hypoxia-associated radioresistance through paradoxically enhanced activation under low oxygen tension.

The demonstrated synergy between radiation and locally-activated doxorubicin not only potentiates tumor cell killing but also establishes feedback amplification loops whether through caspase-3 propagation or ROS-mediated radiosensitization that could address intratumoral heterogeneity more effectively than conventional targeted therapies.

Despite these remarkable advances in radiotherapy triggered prodrug activation approach, translation to clinical practice faces several formidable challenges which includes the following: **(i)** Scalable manufacturing of specialized prodrug conjugates under Good Manufacturing Practices (GMP) conditions remains largely uncharted, particularly for complex multi-component systems involving heterobifunctional linkers or nanomaterial scaffolds.; **(ii)** Standardized dosimetry protocols correlating radiation dose, prodrug concentration, and drug release kinetics are currently lacking, as are comprehensive pharmacokinetic and toxicity profiles in large animal models.

**(iii)** The heterogeneous composition of the tumor microenvironment (TME), immune cell infiltration, and stromal barriers may yield non-uniform activation patterns that compromise therapeutic efficacy.; **(iv)** Regulatory pathways for such combination-activated therapeutics remain ambiguous, requiring coordinated approval frameworks that address both the radiotherapy and prodrug components.; **(v)** Furthermore, the potential for off-target activation by scattered radiation doses to adjacent normal tissues, while minimal, necessitates rigorous radiobiological characterization.

Future prospects lie in developing next-generation prodrug architectures with enhanced radiation sensitivity at lower doses, multi-drug payloads that release synergistic drug combinations sequentially, and integration with advanced radiotherapy modalities such as FLASH therapy or proton therapy for even sharper dose gradients. Incorporating nanocarriers functionalized with targeting ligands could augment tumor accumulation while shielding the prodrug from premature activation, and combination with immune checkpoint inhibitors might exploit radiation-induced immunogenic cell death to create powerful chemo-radio-immunotherapy regimens.

Ultimately, X-ray triggered doxorubicin prodrugs hold transformative potential to redefine the therapeutic index of anthracycline chemotherapy, offering a blueprint for precision combination therapies that could be extended to other chemotherapeutic agents and solid tumor indications, thereby catalyzing a new era of radiation-guided drug delivery with tangible clinical impact.

## 4. Acknowledgements

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## 5. Notes and References


1. F. Bray, M. Laversanne, H. Sung, J. Ferlay, R. L. Siegel, I. Soerjomataram, A. Jemal., *CA Cancer J Clin.* **2024**,74(3): 229-263

2. C.F Thorn, C. Oshiro, S. Marsh, T. H. Boussard, H. McLeod, T. E. Klein, R.B Altman, *Pharmacogenet Genomics*., **2011**, 21(7):440–446.

3. A. N. Linders, I. B. Dias, T. L. Fernández, C. G. Tocchetti, N. Bomer and P. Van der Meer, *npj Aging*, **2024**, volume 10, Article number: 9

4. S. Sritharan, N. Sivalingam, *Life Sciences*, **2021**, 278, 119527, https://doi.org/10.1016/j.lfs.2021.119527

5 K. S. Rallis, T. H. L. Yau, M. Sideris, *Anticancer Res.*, **2021**, 41(1), 1-7. doi: 10.21873/anticanres.14746

6 . J. Delahousse, C. Skarbek, A. Paci, *Cancer Chemotherapy and Pharmacology*, **2019**, 84, 937–958

7. J. Rautio, N. A. Meanwell, L. Di and M. J. Hageman, *Nature Reviews Drug Discovery*, **2018**, 17, 559–587

8. C. Wang, Z. Zhang, and Z. Liu, *ACS Cent. Sci.* **2025**, 11, 1306−1320

9 . X. Chen, J. Song, X. Chen, and H. Yang, *Chem. Soc. Rev.* **2019**, 48, 3073–3101

10. Y. You, Y. Chang, S. Pan, Q. Bu, J. Ling, W. He, and T. Chen, *Angew. Chem. Int. Ed.* **2025**, 64, e202412922

11. Z. Ding, Z. Guo, Y. Zheng, Z. Wang, Q. Fu, and Z. Liu, *J. Am. Chem. Soc.* **2022**, 144, 9458−9464

12. K. Tanabe, M. Sugiura, T. Ito, S. Nishimoto, *Bioorganic & Medicinal Chemistry.* **2012**, 20,17, 5164-5168

13. D. Shao, F. Zhang, F. Chen, X. Zheng, H. Hu, C. Yang, Z. Tu, Z. Wang, Z. Chang, J. Lu, T. Li, Y. Zhang, L. Chen, K. W. Leong, and W. Dong, *Adv. Mater*. **2020**, *32*, 2004385

14. W. Deng, W. Chen, S. Clement, A. Guller, Z. Zhao, A. Engel and E. M. Goldys, *Nat. Comm.* **2018**, 9, 2713

15. D. Schaue and W. H. McBride, *Nature Reviews Clinical Oncology.* **2025**, 12, 527–540

16. H. Zhao, J. Yu, R. Zhang, P. Chen, H. Jiang, W. Yu, *European Journal of Medicinal Chemistry*, **2023**, 258, 115612

17. J. Geng, Y. Zhang, Q. Gao, K. Neumann, H. Dong, H. Porter, M. Potter, H. Ren, D. Argyle, M. Bradley, *Nat Chem.*, **2021**, 13(8): 805–810

18. J. M. Quintana, D. Arboleda, H. Hu, E. Scott, G. Luthria, S. Pai, S. Parangi, R. Weissleder, and M. A. Miller, *Bioconjugate Chem.* **2022**, 33, 1474−1484

19. S. W. Chung, B. S. Lee, J. Choi, S. W. Kim, I. S. Kim, S. Y. Kim, and Y. Byun, *J. Med. Chem.* 2015, 58, 6435−6447