Switching On Prodrugs Using Radiotherapy

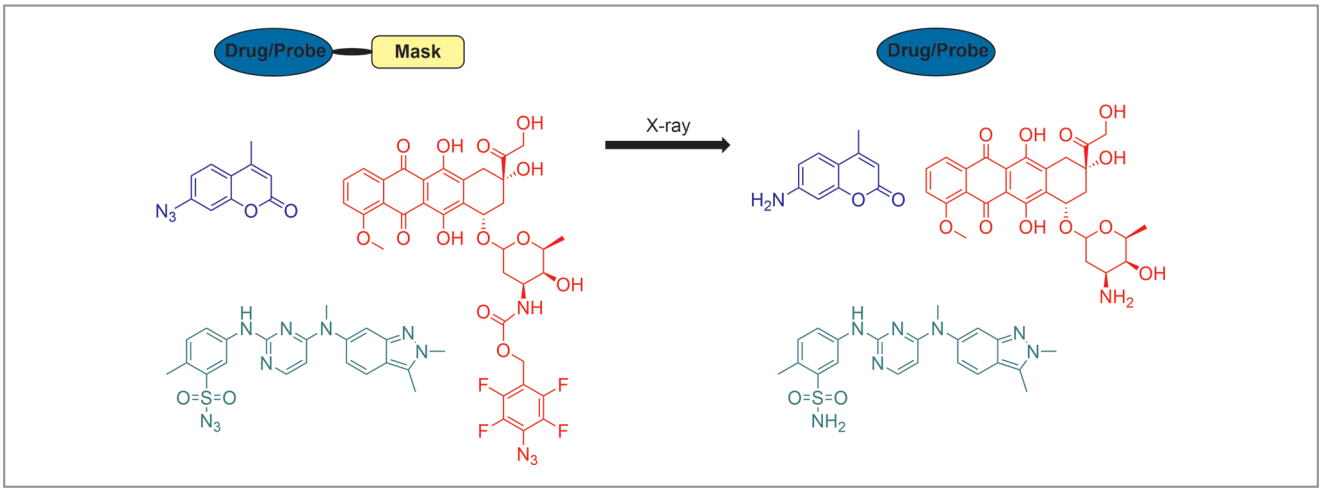
Nat. Chem. **2021**, *13*, 805–810

Chemotherapy is extensively used in oncology, being highly efficient for cancer treatment. However, many commercially applied chemotherapeutic drugs have less-than-ideal selectivity for cancer cells and often do not spare normal healthy tissues/organs, thus giving rise to systemic toxicity effects in patients. The use of prodrugs is known to be an effective strategy to reduce these side effects and enhance selectivity. Prodrugs are typically chemotherapy drugs that have been chemically modified, such that they release the pharmacologically active agent upon chemical modification *in vivo*. Thus, when the prodrugs reach the tumor area, stimulus-triggered de-caging of the 'modification' takes place and releases the active drug, thus achieving precise tumor treatment.

"The stimuli used to activate prodrugs can be divided into two categories, namely internal stimuli and external stimuli," said Professor Jin Geng at Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences (P. R. of China), whose group has a strong interest in this research area. "Internal stimuli include enzymes over-expressed in cancer, or physiological parameters or aberrations found within the tumor microenvironment, such as pH and hypoxia. External stimuli often offer precise temporal and spatial control over site of action. For example, light, ultrasound, heat, and local molecular injections can trigger prodrug activation at the site of disease and at the desired time," he added.

Professor Geng said that since radiotherapy is an effective treatment strategy for inhibiting tumor growth, it is often used in combination with chemotherapy to treat patients suffering from advanced cancers. "Concomitant chemo-radiotherapy for malignant tumors originates from the concept of comprehensive treatment and has become a standard therapeutic method to prolong patients' survival time," he said, adding: "Currently used concomitant treatments use sensitizers to promote the effect of radiotherapy. However, the use of radiotherapy radiation sources, *i.e.* X-rays, as a source of stimuli to activate prodrugs, has only rarely been investigated."

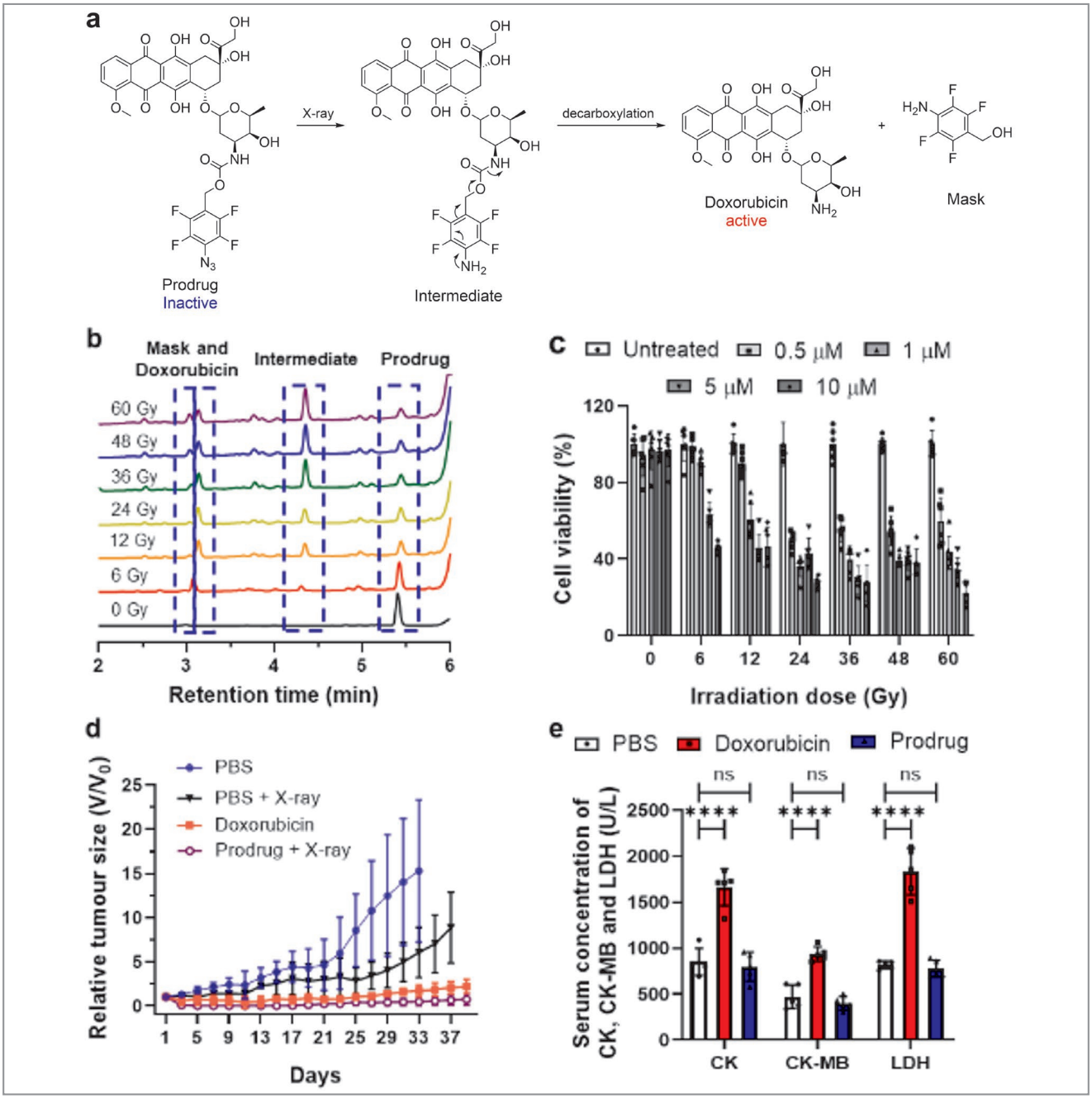
In this collaborative work, the groups of Professor Geng and that of Professor Mark Bradley at the University of Edinburgh (UK) imagined an antitumor drug that could be converted into an X-ray-activatable prodrug with sufficient stability and significantly reduced toxicity compared to the naked drug, such that systemic toxicity issues can be overcome. Professor Geng said: "For patients receiving a dose of such a prodrug, the toxic drug molecules would only be generated at the tumor site, when receiving the X-ray treatment. Additionally, with the development of therapeutic X-ray techniques, precise radiation with high 3D resolution could be achieved, so that the prodrug activation region may be precisely controlled, therefore allowing the use of higher doses of prodrugs in patients, to further improve the treatment's efficacy."



Scheme 1 A coumarin-based quenched fluorophore and pazopanib- and doxorubicin-derived model prodrug molecules were activated by X-ray radiation

  • Published online: December 17, 2021 • DOI: 10.1055/s-0040-1720546

Professor Bradley added: "Here, we have explored the possibility of using clinically utilized radiotherapy X-ray sources to activate antitumor prodrugs. In the early stage of this project, we conducted a wide-range screening of potentially activatable organic molecules that may react following X-ray radiation. Fortunately, we found that sulfonyl azides and fluoroaryl azides can be converted into the corresponding sulfonamides and aromatic amines at clinically relevant doses of

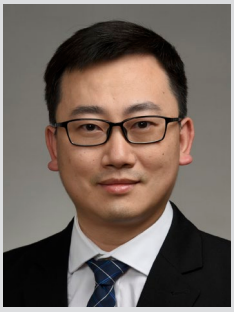


Scheme 2 (a) The reaction of the doxorubicin-based prodrug and mechanistic pathway for liberation of doxorubicin. The activation of the prodrug has been proved on (b) the molecular level, (c) cancer cell lines, and (d) animal models. (e) Biochemical markers CK, CK-MB and LDH levels in plasma showed that the prodrug strategy can effectively reduce side effects in mice.

X-ray radiation with high efficiency. It is reported that X-ray radiation of aqueous solutions can generate reactive species such as hydroxy radicals, hydrogen radicals, and hydrogen peroxide, but here we propose that the azide reduction mechanism occurs through 'solvated electrons'."

To translate these findings to medical applications, the authors introduced a functional group onto antitumor drug molecules (and fluorescent reporters) to synthesize a series of prodrugs and quenched fluorophores. "We verified their activation efficiency, pharmacological activity and biosafety both *in vitro* and in *vivo*," explained Professor Geng. He continued: "We found the prodrugs reduce systemic toxicity while they were efficiently generated at the tumor site, significantly prolonging the survival time of tumor-bearing animals." Professor Bradley concluded: "We believe this X-ray activatable prodrug system could represent an important new modality in therapeutic oncology and open up a new era in targeted and directed cancer chemoradiotherapy."

About the authors

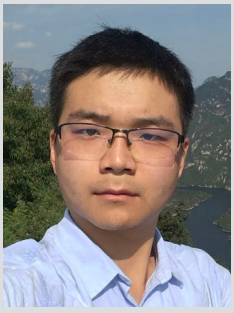


Prof. J. Geng

Jin Geng is a professor of chemistry at Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences (SIAT, P. R. of China). He took up his current position in 2019, following on from his appointment at the University of Edinburgh (UK) as a research fellow working with Professor Mark Bradley. He is the director of the centre for polymers in medicine at SIAT. He leads a diverse team of researchers focusing on polymer chemistry, biomaterials, and biomedicine technologies, and conducts research and development of diagnostic technologies and innovative drugs for tumors and other major diseases.

Dr. Y. Zhang

Yichuan Zhang graduated from the University of Edinburgh (UK) in 2019 and is working as a postdoctoral researcher in Shenzhen (P. R. of China). His research interests include chemical biology and polymer chemistry and he has achieved a series of outstanding outcomes in the field of cancer therapeutic drugs, prodrug activations, and live cell manipulations.



Dr. Q. Gao

Quan Gao received his PhD in biochemistry and molecular biology from the Institute of Microbiology, Chinese Academy of Sciences (Beijing, P. R. of China) in 2019. His doctoral research focused on the antitumor mechanism of fungal secondary metabolites. He is now doing postdoctoral research at Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences (Shenzhen, Guangdong, P. R. of China) under Prof. Jin Geng and studying the antitumor effects of controlled intracellular polymerization.

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 Synform **2022/01**, A14–A18 • Published online: December 17, 2021 • DOI: 10.1055/s-0040-1720546

Prof. K. Neumann

Kevin Neumann is an Assistant Professor (tenure track) at Radboud University, The Netherlands. His research focuses on new principles for drug activation and delivery. In 2018, Kevin obtained his PhD at the University of Edinburgh (UK), under the supervision of Professor Mark Bradley. In his PhD, Kevin worked on tetrazine-mediated prodrug activation chemistry. It was during this time when Kevin joined the project of radiotherapy-mediated prodrug activation. For his postdoctoral studies, Kevin joined the group of Professor Jeffrey Bode at ETH Zurich, Switzerland. There, he worked on the total chemical synthesis of proteins and their biological evaluation.

Dr. H. Dong

Hua Dong was born in 1985, in Nancheng, Sichuan Province (P. R. of China). He received his doctorate in physical chemistry from the Institute of Chemistry of the Chinese Academy of Sciences (P. R. of China) in 2012. After two postdoctoral studies at the University of Barcelona in Spain and the University of Edinburgh in the UK, he joined the School of Materials and Chemical Engineering at Chengdu Polytechnic University in 2018. At present, he is mainly engaged in special immersion interface material design preparation and application research.

Prof. H. Porter

Hamish Porter is a medical radiation physicist who was Consultant Clinical Physicist and Deputy Head of Oncology Physics at Edinburgh Cancer Centre (UK). He studied chemistry and physics at Edinburgh University (UK) and has held postdoctoral and academic posts at the Universities of Stirling (UK), UMIST (Manchester, UK), London (ICR, UK), Carnegie Mellon University (USA), Oxford (Balliol College; UK) and Edinburgh (UK). Oxford projects involved the development of UV and X-ray photoelectron microscopy with Professor D. W. Turner F.R.S. He was 2011 Silvanus Thompson medallist of the British Institute of Radiology for developments in electron linear accelerators for cancer therapies. He has worked as a physics consultant to several private Radiation Oncology Centres and four University Veterinary Oncology Centres. His present research centers on clinical radiobiology/radiochemistry of relativistic electron and proton beams.

Mr. M. Potter

Mark Potter is a Consultant Colorectal Surgeon at the Western General Hospital, Edinburgh (UK). This is a dedicated Colorectal Unit, serving the population of Edinburgh and tertiary referral practice from all areas of Scotland. The Unit is one of the largest in Europe and has an international research reputation. He was awarded BSc in chemistry before reading medicine at the University of Edinburgh (UK). His MD thesis was looking for novel ways of detecting colorectal cancer mutations in clinical samples. He is an Honorary Clinical Senior Lecturer at the University of Edinburgh and Fellow of the Royal College of Surgeons of England and Edinburgh. He is a member of the European Society of Coloproctology (ESCP) Education Committee. His current research interests include translational studies for surgical technology, targeted chemotherapy and anastomotic leak.

Prof. H. Ren

Hua Ren received his master's and doctoral degrees from The Beijing Concord Medical College (P. R. of China) in 2004 and 2010, respectively. He was a radiotherapist at Oncology Hospital of the Chinese Academy of Medical Sciences (P. R. of China, 1997–2021) and was hired as an associate professor at Southern University of Science and Technology (P. R. of China in 2020. His research interest includes cancer and radiation therapy.

David Argyle graduated from the University of Glasgow (UK) veterinary school and subsequently worked in general practice. He returned to Glasgow to complete a PhD in the Department of Veterinary Pathology and then worked as a lecturer and senior lecturer in clinical oncology in the Department of Clinical Studies. In 2002, he became associate professor of clinical oncology at the University of Wisconsin-Madison, USA. In 2005, he returned to the UK to take the William Dick Chair of Clinical Studies at the University of Edinburgh. On his return he set up the R(D)SVS Cancer and Imaging Centre. He in an RCVS and European Specialist in Veterinary Oncology, a Diplomat of the European College of Internal Medicine in Oncology and is co-scientific editor of the Journal of Veterinary and Compara-

tive Oncology. Within the R(D)SVS he is the Dean of Veterinary Medicine and Head of School and is also the Deputy Head of The College of Medicine and Veterinary Medicine. He has overall responsibility for the School including its research arm, the Roslin Institute. In 2016, he was elected Fellow of the Royal Society of Edinburgh. In the same year, he was elected Fellow of the Royal College of Veterinary Surgeons (for meritorious contributions to veterinary research).

Prof. M. Bradley

Mark Bradley, based at the University of Edinburgh (UK), is a chemist by training but with a strong interdisciplinary ethos and translational mindset. He began his academic career in 1992 at the University of Southampton (UK) as a Royal Society University Research Fellow, where he worked in the area of combinatorial chemistry, co-founding Ilika Technologies. He moved to the University of Edinburgh in 2005 where over the years he has been co-founder of Edinburgh Molecular Imaging, DestiNA Genomics and most recently BioCativa. He has published some 400 papers and reviews and 25 patents and is an ERC Advanced grant awardee.

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