

## Photoactive platinum(IV) complex conjugated to a cancer-cell-targeting cyclic peptide

Shi, Huayun; Wang, Qian; Venkatesh, V; Feng, Guokai; Young, Lawrence S; Romero-Canelón, Isolda; Zeng, Musheng; Sadler, Peter J.

DOI:

[10.1039/C9DT00909D](https://doi.org/10.1039/C9DT00909D)

License:

Creative Commons: Attribution (CC BY)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Shi, H, Wang, Q, Venkatesh, V, Feng, G, Young, LS, Romero-Canelón, I, Zeng, M & Sadler, PJ 2019, 'Photoactive platinum(IV) complex conjugated to a cancer-cell-targeting cyclic peptide', *Dalton Transactions*, vol. 48, no. 24, pp. 8560-8564. <https://doi.org/10.1039/C9DT00909D>

[Link to publication on Research at Birmingham portal](#)

### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

Cite this: *Dalton Trans.*, 2019, **48**, 8560Received 28th February 2019,  
Accepted 26th April 2019

DOI: 10.1039/c9dt00909d

rsc.li/dalton

## Photoactive platinum(IV) complex conjugated to a cancer-cell-targeting cyclic peptide†

Huayun Shi,<sup>a</sup> Qian Wang,<sup>b</sup> V. Venkatesh,<sup>a</sup> Guokai Feng,<sup>b</sup> Lawrence S. Young,<sup>c</sup> Isolda Romero-Canelón,<sup>a,d</sup> Musheng Zeng<sup>b</sup> and Peter J. Sadler<sup>\*,a</sup>

A conjugate of cancer-cell targeting cyclic disulphide nonapeptide c(CRWYDENAC) consisting of nine L-amino acids with the photoactive succinate platinum(IV) complex *trans,trans*-[Pt(N<sub>3</sub>)<sub>2</sub>(py)<sub>2</sub>(OH)(succinate)] (Pt-cP) has been synthesised and characterised. The conjugate was stable in dark, but released succinate-peptide and Pt(II) species upon irradiation with visible light, and formed photoproducts with guanine. Conjugate Pt-cP exhibited higher photocytotoxicity than parent complex *trans,trans*-[Pt(N<sub>3</sub>)<sub>2</sub>(OH)<sub>2</sub>(py)<sub>2</sub>] (FM-190) towards cancer cells, including ovarian A2780, lung A549 and prostate PC3 human cancer cells upon irradiation with blue light (465 nm, 17.28 J cm<sup>-2</sup>) with IC<sub>50</sub> values of 2.8–22.4 μM and the highest potency for A549 cells. Even though the dark cellular accumulation of Pt-cP in A2780 cells was lower than that of parent FM-190, Pt from Pt-cP accumulated in cancer cells upon irradiation to a level >3x higher than that from FM-190. In addition, the cellular accumulation of Pt from Pt-cP was enhanced ca. 47x after irradiation.

Photoactive diazido platinum(IV) prodrugs offer potential for improved treatment of cancer due to their high stability and low toxicity in the dark, potent photocytotoxicity, and novel mechanism of action which has the possibility to overcome cisplatin resistance in cancer cells.<sup>1–6</sup> Among them, *trans,trans*-[Pt(N<sub>3</sub>)<sub>2</sub>(OH)<sub>2</sub>(py)<sub>2</sub>] (FM-190) is a promising prodrug candidate,<sup>7</sup> which can be activated by visible light with a high photocytotoxicity index. Derivatisation of the detachable axial ligands in platinum(IV) prodrugs is now a common strategy to enhance their pharmacological properties.<sup>8–12</sup> For example,

conjugation of FM-190 to α<sub>v</sub>β<sub>3</sub> and α<sub>v</sub>β<sub>5</sub> integrin-selective RGD-containing peptides introduces a preference towards SK-MEL-28 melanoma cancer cells that overexpress the α<sub>v</sub>β<sub>3</sub> integrin,<sup>13</sup> and incorporation of a TEMPO radical can enhance the photocytotoxicity.<sup>14</sup> FM-190 has also been conjugated to drug delivery upconversion-luminescent nanoparticles,<sup>15</sup> hydrogels,<sup>16</sup> and block copolymer micelles<sup>17</sup> for activation with longer wavelength and improved selectivity.

Integrins are not only transmembrane receptors that facilitate cell-cell and cell-matrix adhesion,<sup>18–20</sup> but also regulators of cancer progression signalling pathways.<sup>21</sup> Thus, integrins play an important role in cancer progression and metastasis. The overexpression of integrins on cancer cells provides a useful diagnostic and therapeutic avenue to cancer therapy.<sup>22–25</sup> The integrin α6 receptor is reported to be overexpressed in various cancer cell lines,<sup>26–28</sup> including ovarian, lung, prostate and other cancers, and promotes the migration, invasion and survival of cancer cells.

The tumour-specific homing cyclic peptide c(CRWYDENAC) targets the integrin α6 receptor, using the sequence RWY (Arg-Trp-Tyr) as binding site.<sup>29</sup> RWY-grafted polymeric nanoparticles encapsulating a cisplatin prodrug display a 100-fold increase in cytotoxicity towards integrin α6-overexpressing nasopharyngeal carcinoma compared to free cisplatin.<sup>29</sup>

Here we have synthesised and characterised Pt-cP, a conjugate of a photoactive *trans*-diazido platinum(IV) complex with the cyclic peptide c(CRWYDENAC), *via* amide bond formation between the free carboxyl group of the Pt-bound axial succinate and the N-terminal amino group of the peptide. All of amino acids in the peptide have the L-configuration. Photodecomposition and photoreactions with the nucleotide guanosine 5'-monophosphate (5'-GMP) were investigated, since guanine bases are potential DNA targets for Pt(II) photoproducts. The photocytotoxicity and cellular accumulation in integrin α6-overexpressing cancer cell lines were studied in comparison with the parent complex FM-190. We show that the incorporation of the cyclic peptide as an axial ligand enhanced the photocytotoxicity and cancer cellular accumulation of this photoactive diazido platinum(IV) prodrug.

<sup>a</sup>Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK.  
E-mail: p.j.sadler@warwick.ac.uk

<sup>b</sup>State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University Cancer Center, Guangzhou 510060, China

<sup>c</sup>Medical School, University of Warwick, Coventry CV4 7AL, UK

<sup>d</sup>School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Birmingham B15 2TT, UK

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9dt00909d

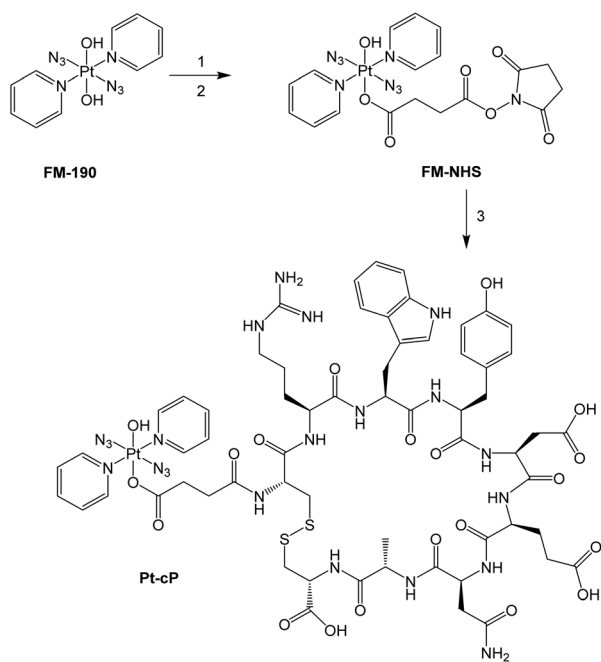


The synthetic route for photoactive platinum(IV) complex **Pt-cP** is summarised in Scheme 1. **FM-NHS** was prepared according to a procedure similar to that reported previously.<sup>15</sup> The *N*-hydroxysuccinimide (NHS) active ester of *trans,trans,trans*-[Pt(N<sub>3</sub>)<sub>2</sub>(py)<sub>2</sub>(OH)(succinate)] with one axial carboxyl group was prepared by reaction with EDC, NHS and DMAP to generate **FM-NHS** and purified by column chromatography on silica gel. The coupling was carried out by stirring freshly prepared **FM-NHS** with cyclic peptide c(CRWYDENAC) in DMF with DIPEA under nitrogen for 36 h. The resulting yellow solid possessed good HPLC purity (94%, Fig. S1, ESI<sup>†</sup>), and was characterised by ESI-HRMS, <sup>1</sup>H NMR and UV-vis spectroscopy. The

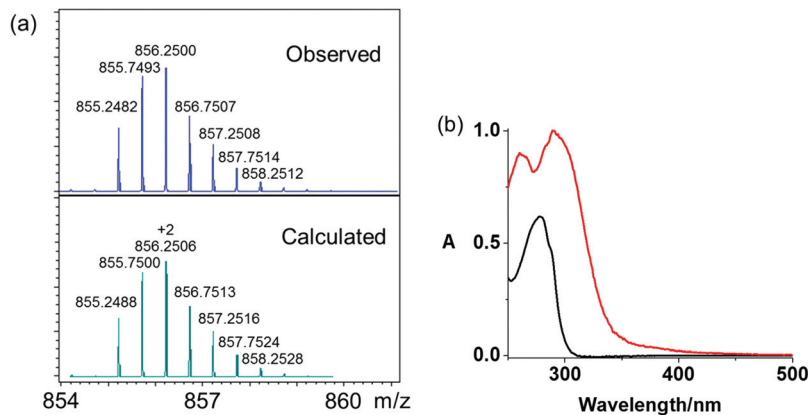
ions [M + 2H]<sup>2+</sup> (855.7493) and [M + H]<sup>+</sup> (1710.4919) were detected by HR-MS (Fig. 1a and Fig. S2, ESI<sup>†</sup>). The *m/z* values and the isotopic mass distribution pattern of Pt are in good agreement with the calculated spectra. A full assignment of the <sup>1</sup>H NMR peaks for the cyclic peptide peptide in DMSO-*d*<sub>6</sub> was not attempted, but the doublet at 8.81 ppm (*J* = 5.4 Hz) and the triplets at 8.25 ppm (*J* = 7.6 Hz) and 7.81 ppm (*J* = 6.6 Hz) can be assigned to the α, γ and β protons, respectively, of the pyridine ligands (Fig. S3, ESI<sup>†</sup>). The singlet at 10.7 ppm is ascribed to the NH of the Trp indole ring and the NH amide proton signals appear between 6.5 and 9.0 ppm. In addition, in a mixture of 80% DMSO-*d*<sub>6</sub> and 20% D<sub>2</sub>O (v/v), aromatic protons assigned to pyridine, and Trp and Tyr amino acid residues confirm the conjugation of the Pt(IV) fragment to the cyclic peptide (Fig. S4, ESI<sup>†</sup>). The absorption band at 290 nm (30 435 M<sup>-1</sup> cm<sup>-1</sup>) for **Pt-cP** in phenol red-free RPMI-1640 cell culture medium with 5% DMSO (v/v) present to aid solubility, is mainly assignable to a LMCT (N<sub>3</sub> → Pt<sup>IV</sup>) transition (Fig. 1b). The cyclic peptide displayed an absorption band at 278 nm due to Trp and Tyr side chains, and also contributed to the absorption band for **Pt-cP** at 290 nm.

The dark stability and photodecomposition of **Pt-cP** in phenol red-free RPMI-1640 were monitored by UV-vis spectroscopy. The absorption spectra of **Pt-cP** exhibited little change in the dark over 2 h, indicating its dark stability (Fig. 2a). However, a gradual decrease in intensity of absorption at 290 nm was observed upon irradiation with blue light (420 nm), which suggested the photo-reduction of Pt(IV) to Pt(II) and release of azide ligands (Fig. 2b).

The photoproducts from reactions of **Pt-cP** and 5'-GMP (guanosine 5'-monophosphate) were investigated by LC-MS (Fig. S5 and Table S1, ESI<sup>†</sup>). An aqueous solution of **Pt-cP** (30 μM) and 2 mol equiv. of 5'-GMP was irradiated with blue light (420 nm) for 1 h at 298 K. Then the products were analysed by reverse-phase LC-MS. Upon 1 h irradiation, the peak assigned as **Pt-cP** (retention time = 12.7 min) disappeared and the intact succinate-c(CRWYDENAC) moiety (*m/z* = 1257.28) was released (Fig. S5<sup>†</sup>). The Pt-GMP adducts

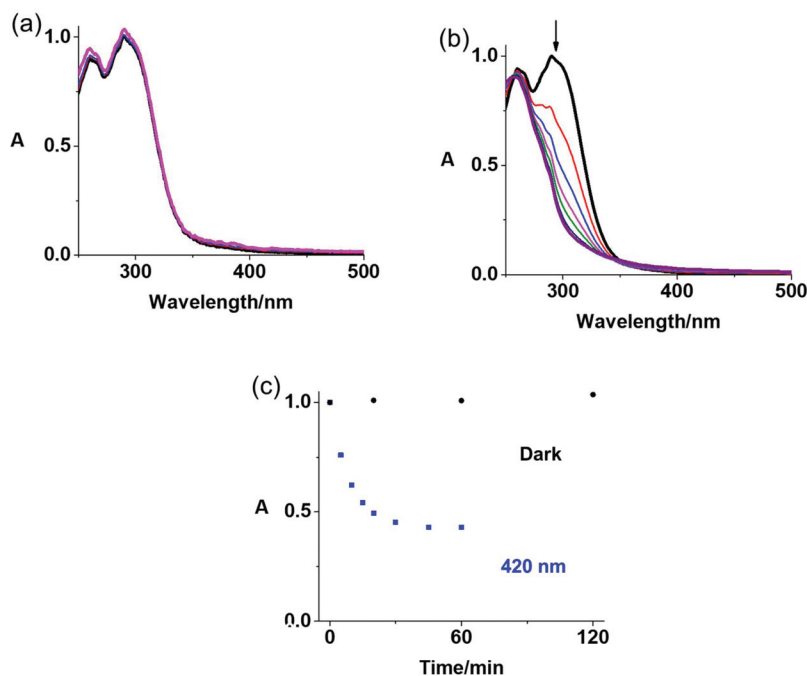


**Scheme 1** The synthetic route for photoactive conjugate **Pt-cP**. (1) Succinic anhydride, DMF, 348 K, overnight; (2) EDC, NHS, DMAP, DMF, N<sub>2</sub>, 298 K, overnight; (3) c(CRWYDENAC), DIPEA, DMF, N<sub>2</sub>, 298 K, 36 h.



**Fig. 1** (a) Observed and calculated HR-ESI mass spectra for the molecular ion [M + 2H]<sup>2+</sup> of **Pt-cP**; (b) UV-vis spectra of the conjugate **Pt-cP** (red) and the free cyclic peptide (black) in phenol red-free RPMI-1640 cell culture medium at 298 K.





**Fig. 2** (a) Dark stability over 2 h and (b) photodecomposition with blue light (420 nm, over 1 h) of conjugate **Pt-cP** in phenol red-free RPMI-1640 determined by UV-vis spectroscopy; (c) time dependence of the absorbance at 290 nm.

$\{\text{Pt}^{\text{II}}(\text{N}_3)(\text{py})_2(\text{GMP})\}^+$  (758.22) and  $\{\text{Pt}^{\text{II}}(\text{OC}(\text{O})\text{H})(\text{py})_2(\text{GMP})\}^+$  (762.16) were detected (GMP in MS formula is considered neutral unless otherwise stated, and the formic acid arises from the mobile phase). No apparent differences between the Pt-GMP adducts formed by the photoreaction between **Pt-cP** and 5'-GMP compared with similar reactions of the parent complex **FM-190** were observed, which suggested that conjugation of cyclic peptide in an axial position did not affect the photochemical reactions of the platinum(IV) centre and binding to the DNA/RNA base guanine after irradiation.<sup>7</sup>

Conjugate **Pt-cP** exhibited promising dark stability and photocytotoxicity towards several human cancer cell lines, including A2780 ovarian, A549 lung and PC3 prostate human cancer cell lines. The dose-dependent inhibition of cell viability determined by the sulforhodamine B (SRB) colorimetric assay for conjugate **Pt-cP** in comparison with the parent complex **FM-190** both in the dark and after irradiation, is summarised in Table 1. Both complexes were relatively non-toxic towards all cancer cell lines in the dark with  $\text{IC}_{50}$  values  $>100 \mu\text{M}$ . However, the cytotoxicity of both complexes was significantly enhanced after 1 h irradiation with blue light (465 nm,  $17.28 \text{ J cm}^{-2}$ ). Importantly, the photocytotoxicity of conjugate **Pt-cP** ( $\text{IC}_{50} = 6.6 \mu\text{M}$  for A2780,  $2.8 \mu\text{M}$  for A549, and  $22.4 \mu\text{M}$  for PC3) was greater than that of the parent complex **FM-190** ( $\text{IC}_{50} = 7.1 \mu\text{M}$  for A2780,  $51.9 \mu\text{M}$  for A549, and  $55.6 \mu\text{M}$  for PC3) with photocytotoxicity indices (PI) of  $>15.2$ ,  $35.7$  and  $4.5$  towards A2780 ovarian, A549 lung and PC3 prostate cancer cells, respectively. These results indicate that the conjugation with the cyclic peptide c(CRWYDENAC) enhances the photocytotoxicity of this platinum(IV) prodrug without

**Table 1**  $\text{IC}_{50}$  values and photocytotoxicity indices (PI) for conjugate **Pt-cP** and the parent complex **FM-190** obtained after 1 h incubation, 1 h irradiation (465 nm) and 24 h recovery. CDDP (cisplatin) was used as a reference

Cell line		$\text{IC}_{50}^a$ ( $\mu\text{M}$ )		
		<b>Pt-cP</b>	<b>FM-190</b>	<b>CDDP</b>
A2780	Dark	$>100$	$>100^b$	$>100^b$
	Irrad.	$6.6 \pm 0.2$	$7.1 \pm 0.4^b$	$>100^b$
	PI	$>15.2$	$>14.1$	—
A549	Dark	$>100$	$>100$	$>100$
	Irrad.	$2.8 \pm 0.2$	$51.9 \pm 2.5$	$>100$
	PI	$>35.7$	$>1.9$	—
PC3	Dark	$>100$	$>100$	$>100$
	Irrad.	$22.4 \pm 2.2$	$55.6 \pm 0.9$	$>100$
	PI	$>4.5$	$>1.8$	—
MRC5	Dark	$>100$	$>100^b$	$>100^b$

<sup>a</sup> Data are from three independent experiments. <sup>b</sup> Data are adapted from ref. 14 and 30.

reducing its dark stability. Notably, under the conditions used (short treatment times), the clinical drug cisplatin was inactive (Table 1). Low dark cytotoxicity ( $\text{IC}_{50} > 100 \mu\text{M}$ ) of **Pt-cP** in healthy MRC5 lung cells was observed, which might allow selectivity towards cancer cells to be achieved by spatially-directed irradiation (Table 1).

Cellular accumulation of metallodrugs often plays an important role in their antiproliferative potency. Pt accumulation by A2780 ovarian and A549 lung cancer cells in the dark was investigated when they were exposed to photoactive platinum(IV) complexes at the same Pt concentration ( $10 \mu\text{M}$ ) for



**Table 2** Cell accumulation of Pt (ng per 10<sup>6</sup> cells) in cancer cells after exposure to conjugate **Pt-cP** and the parent complex **FM-190** (10 μM, 1 h dark incubation)

	Platinum accumulation (ng per 10 <sup>6</sup> cells) <sup>a</sup>	
	A2780	A549
<b>Pt-cP</b>	0.17 ± 0.02**	2.5 ± 0.2*
<b>FM-190</b>	1.19 ± 0.04***	1.0 ± 0.2*

<sup>a</sup> All data were determined from triplicate samples and their statistical significance evaluated by a two-tail *t*-test with unequal variances. \**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001.

1 h (Table 2). The cellular accumulation of Pt from conjugate **Pt-cP** (2.5 ng per 10<sup>6</sup> cells) in A549 cells was 2.5× higher than that from the parent complex, which is consistent with the high photocytotoxicity of the conjugate in A549 cells. In contrast, a very low Pt accumulation was detected in A2780 cells after treatment with **Pt-cP** (0.17 ng per 10<sup>6</sup> cells). For comparison, parent complex **FM-190** exhibited similar accumulation in both cell lines, which indicates the selectivity of the conjugate. However, similar photocytotoxicity was observed for **Pt-cP** and **FM-190** in A2780 cells.

To investigate the effect of light exposure on accumulation, duplicate plates of A2780 ovarian cancer cells were exposed to conjugate **Pt-cP** for 1 h in the dark at the IC<sub>50</sub> concentration (6.6 μM). Then some plates were irradiated with blue light (465 nm) for 1 h, while other plates treated with the same drug were left in the dark for comparison (Table 3). It is notable that the cellular accumulation of Pt was *ca.* 47× enhanced after irradiation (9.4 ng Pt per 10<sup>6</sup> cells after irradiation, 0.2 ng Pt per 10<sup>6</sup> cells in the dark), probably because the Pt(II) photo-products are more reactive towards intracellular biomolecules than the Pt(IV) prodrug and were less readily effluxed from the cells.<sup>31</sup> In addition, the cellular accumulation of parent complex **FM-190** (as Pt) in the absence of light (0.9 ng Pt per 10<sup>6</sup> cells) was *ca.* 3× higher than in the presence of light (2.7 ng Pt per 10<sup>6</sup> cells), on treatment of cells at IC<sub>50</sub> concentration (7.1 μM). Platinum accumulation of the conjugate was lower than that of the parent complex before irradiation. However, the amount of Pt from conjugate **Pt-cP** accumulated in A2780 cells is >3× higher than that from parent complex **FM-190** (Table 3) after irradiation. This increased accumulation

**Table 3** Accumulation of Pt (ng per 10<sup>6</sup> cells) in A2780 ovarian cancer cells after exposure to conjugate **Pt-cP** and the parent complex **FM-190** (equipotent IC<sub>50</sub> concentrations, 2 h in dark, or 1 h incubation and 1 h irradiation (465 nm))

	Platinum accumulation (ng per 10 <sup>6</sup> cells) <sup>a</sup>	
	Dark	Irradiated
<b>Pt-cP</b>	0.20 ± 0.03*	9.41 ± 0.03***
<b>FM-190</b>	0.9 ± 0.2*	2.7 ± 0.1***

<sup>a</sup> All data were determined from triplicate samples and their statistical significance evaluated by a two-tail *t*-test with unequal variances. \**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001.

resulted in the similar photocytotoxicity of conjugate **Pt-cP** with **FM-190**, and suggested that the cyclic peptide might deliver Pt to different parts of the cell compared to **FM-190** alone, as anticipated.

In summary, we have prepared and characterised a photo-active conjugate between a *trans*-diazido platinum(IV) prodrug and a receptor-targeting cyclic RWY (Arg-Trp-Tyr) nona-peptide **Pt-cP**. The conjugate exhibited high dark stability, but was potently photocytotoxic towards several human cancer cell lines with IC<sub>50</sub> values of 2.8–22.4 μM. The highest photocytotoxicity and accumulation of the conjugate was observed for A549 cells. Light irradiation promoted the cellular accumulation of Pt from **Pt-cP** significantly (*ca.* 3× that of parent prodrug **FM-190**). This work suggests that cancer cell-targeting cyclic peptides can improve the photo-cytotoxicity and photo-accumulation of photoactive platinum(IV) complexes, and their photo-selectivity towards cancer cells.

## Conflicts of interest

Peptide cP is the subject of US patent US9809622B2.

## Acknowledgements

This research was supported by the EPSRC (grants EP/G006792, EP/F034210/1 to PJS), ERC (grant 247450 to PJS), a Chancellor's International PhD Scholarship from the University of Warwick (for HS), and the Royal Society (grant no. IE131109 for LSY, Newton International Fellowship and follow-on funding AL170006\1 for VV). We also thank Dr Lijiang Song for his help with mass spectrometry.

## References

- M. Imran, W. Ayub, I. S. Butler and Z. ur-Rehman, *Coord. Chem. Rev.*, 2018, **376**, 405–429.
- K. Mitra, *Dalton Trans.*, 2016, **45**, 19157–19171.
- P. Müller, B. Schröder, J. A. Parkinson, N. A. Kratochwil, R. A. Coxall, A. Parkin, S. Parsons and P. J. Sadler, *Angew. Chem., Int. Ed.*, 2003, **42**, 335–339.
- F. S. Mackay, J. A. Woods, P. Heringová, J. Kašpárková, A. M. Pizarro, S. A. Moggach, S. Parsons, V. Brabec and P. J. Sadler, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 20743–20748.
- Y. Zhao, N. J. Farrer, H. Li, J. S. Butler, R. J. McQuitty, A. Habtemariam, F. Wang and P. J. Sadler, *Angew. Chem., Int. Ed.*, 2013, **52**, 13633–13637.
- J. Kasparkova, H. Kostrhunova, O. Novakova, R. Křikavová, J. Vančo, Z. Trávníček and V. Brabec, *Angew. Chem., Int. Ed.*, 2015, **54**, 14478–14482.
- N. J. Farrer, J. A. Woods, L. Salassa, Y. Zhao, K. S. Robinson, G. Clarkson, F. S. Mackay and P. J. Sadler, *Angew. Chem., Int. Ed.*, 2010, **49**, 8905–8908.
- T. C. Johnstone, K. Suntharalingam and S. J. Lippard, *Chem. Rev.*, 2016, **116**, 3436–3486.



- 9 Y. Yuan, R. T. K. Kwok, B. Tang and B. Liu, *J. Am. Chem. Soc.*, 2014, **136**, 2546–2554.
- 10 Y. Zheng, K. Suntharalingam, T. C. Johnstone, H. Yoo, W. Lin, J. G. Brooks and S. J. Lippard, *J. Am. Chem. Soc.*, 2014, **136**, 8790–8798.
- 11 S. G. Awuah, Y. Zheng, P. M. Bruno, M. T. Hemann and S. J. Lippard, *J. Am. Chem. Soc.*, 2015, **137**, 14854–14857.
- 12 E. Petruzzella, J. P. Braude, J. R. Aldrich-Wright, V. Gandin and D. Gibson, *Angew. Chem., Int. Ed.*, 2017, **56**, 11539–11544.
- 13 A. Gandioso, E. Shaili, A. Massaguier, G. Artigas, A. González-Cantó, J. A. Woods, P. J. Sadler and V. Marchán, *Chem. Commun.*, 2015, **51**, 9169–9172.
- 14 V. Venkatesh, C. J. Wedge, I. Romero-Canelón, A. Habtemariam and P. J. Sadler, *Dalton Trans.*, 2016, **45**, 13034–13037.
- 15 Y. Min, J. Li, F. Liu, E. K. L. Yeow and B. Xing, *Angew. Chem., Int. Ed.*, 2014, **53**, 1012–1016.
- 16 V. Venkatesh, N. K. Mishra, I. Romero-Canelón, R. R. Vernooij, H. Shi, J. P. C. Coverdale, A. Habtemariam, S. Verma and P. J. Sadler, *J. Am. Chem. Soc.*, 2017, **139**, 5656–5659.
- 17 D. Zhou, J. Guo, G. B. Kim, J. Li, X. Chen, J. Yang and Y. Huang, *Adv. Healthcare Mater.*, 2016, **5**, 2493–2499.
- 18 R. O. Hynes, *Cell*, 1992, **69**, 11–25.
- 19 J. S. Desgrosellier and D. A. Cheresch, *Nat. Rev. Cancer*, 2010, **10**, 9–22.
- 20 Y. H. Soung, H. J. Gil, J. L. Clifford and J. Chung, *Curr. Protein Pept. Sci.*, 2011, **12**, 23–29.
- 21 A. E. Aplin, A. K. Howe and R. L. Juliano, *Curr. Opin. Cell Biol.*, 1999, **11**, 737–744.
- 22 J. R. Marthick and J. L. Dickinson, *Prostate Cancer*, 2012, **2012**, 298732.
- 23 C. W. Huang, Z. Li, H. Cai, T. Shahinian and P. S. Conti, *Mol. Imaging*, 2011, **10**, 284–294.
- 24 A. Massaguier, A. González-Cantó, E. Escribano, S. Barrabés, G. Artigas, V. Moreno and V. Marchán, *Dalton Trans.*, 2015, **44**, 202–212.
- 25 L. Wei, F. Yin, W. Zhang and L. Li, *Medicine*, 2017, **96**(12), e6345.
- 26 Z. T. Colburn and J. C. R. Jones, *Am. J. Respir. Cell Mol. Biol.*, 2017, **56**(4), 443–452.
- 27 I. C. Sroka, H. Chopra, L. Das, J. M. C. Gard, R. B. Nagle and A. E. Cress, *J. Cell. Biochem.*, 2016, **117**(2), 491–499.
- 28 L. Das, T. A. Anderson, J. M. C. Gard, I. C. Sroka, S. R. Strautman, R. B. Nagle, C. Morrissey, B. S. Knudsen and A. E. Cress, *J. Cell. Biochem.*, 2017, **118**(5), 1038–1049.
- 29 G. Feng, M. Zhang, H. Wang, J. Cai, S. Chen, Q. Wang, J. Gong, K. W. Leong, J. Wang, X. Zhang and M. Zeng, *Adv. Therap.*, 2019, 1900018.
- 30 H. Shi, I. Romero-Canelón, M. Hreusova, O. Novakova, V. Venkatesh, A. Habtemariam, G. J. Clarkson, J. Song, V. Brabec and P. J. Sadler, *Inorg. Chem.*, 2018, **57**, 14409–14420.
- 31 D. Guo, S. Xu, Y. Huang, H. Jiang, W. Yasen, N. Wang, Y. Su, J. Qian, J. Li, C. Zhang and X. Zhu, *Biomaterials*, 2018, **177**, 67–77.

