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Molecular Cancer Therapeutics

Letter to the Editor

PDT with a Glucose-Conjugated Chlorin for GIST—Letter

Mark Linch[1] and Andrew J. Hayes[2]

Tanaka and colleagues (1) present results of a novel glucose-conjugated photodynamic therapy (PDT) sensitizing agent (H_2TFPC-SGlc) in gastrointestinal stromal tumor (GIST) cells (1). They state that, aside from surgery, there are currently no effective treatment strategies for GIST and demonstrate that there is selective accumulation of H_2TFPC-SGlc– and PDT-induced apoptosis in GIST-T1 cells, possibly as a consequence of increased expression of glucose transporters.

Treatment of patients with GIST using the tyrosine kinase inhibitor (TKI) imatinib heralded the targeted therapeutic era in solid tumors and the sequential use of the TKIs imatinib, sunitinib, and regorafenib has dramatically improved life expectancy (2). These agents are effective because most GISTs carry activating mutations of the c-KIT or platelet-derived growth factor receptor α tyrosine kinases. Resistance to imatinib may be due to *de novo* mutations or acquired mutations during therapy. For localized disease, surgery provides an excellent chance of cure, which is further enhanced by adjuvant imatinib (92% 5-year survival; ref. 3). This knowledge is critical when selecting patient therapy and for developing models to test PDT in GIST. Possible positioning for PDT in the treatment paradigm of GIST would be as an alternative to radiofrequency ablation or surgery in patients with a single site of progressing metastatic disease, in the context of imatinib-resistant mutant clonal outgrowth. Contrary to the report by Tanaka and colleagues, there are numerous GIST cell lines that grow as xenografts (4), enabling PDT to be tested in a clinically relevant mutational background.

Tanaka and colleagues (1) were unable to demonstrate a functional association between GLUT1/3/4 expression and cellular uptake of H_2TFPC-SGlc as RNAi knockdown of GLUT isoforms did not demonstrate any phenotype (1). The explanation was possible redundancy between the GLUT isoforms, but combination knockdowns were not presented, nor were chemical inhibitor studies attempted using pan-GLUT inhibitors. Interestingly, imatinib is reported to be a GLUT inhibitor and investigation of PDT in combination with imatinib may provide insights as to the role of GLUTs in H_2TFPC-SGlc selectivity and whether concomitant treatment should be avoided, potentially informing treatment scheduling. Furthermore, it is not clear why the authors omitted to study GLUT2 as this has previously been cited as the main GLUT in GIST (5).

In summary, Tanaka and colleagues present an interesting new therapy for GIST but to take this forward, the models used to test this intervention should reflect the current molecular understanding and treatment paradigms of GIST.

[1]Department of Oncology, University College London Hospital, London, United Kingdom. [2]Department of Surgical Oncology, Sarcoma Unit, Royal Marsden Hospital, London, United Kingdom.

Corresponding Author: Mark Linch, University College London Hospital, 250 Euston Road, London, NW1 2PG, United Kingdom. Phone: 44-0-203-4479287; E-mail: mark.linch@uclh.nhs.uk

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No potential conflicts of interest were disclosed.

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