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Use of Au-functionalized devices for the specific activation of a bioorthogonal Belinostat prodrug

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Introduction In the last decade, abiotic transition metals have been successfully used for different applications in, on and outside cells, e.g. for the synthesis of small molecules, the functionalization and uncaging of enzymes and *in situ* prodrug activation.(1) Regarding the latter, our group has explored new chemistries and deactivation strategies to develop novel caged chemotherapeutic agents that are specifically released *via*heterogeneous metal catalysis in order to minimize adverse effects associated to chemotherapy.(2) In this communication, we report the development of a bioorthogonal prodrug of the histone deacetylase inhibitor Belinostat and its specific activation *via* biocompatible Au-functionalized resins in cancer cell culture.

Method *O*-alkylated hydroxamate of Belinostat (**2a**) was synthesised by treatment of Belinostat with the corresponding alkyl bromide in the presence of DBU at room temperature for 24 h. Solid supported gold catalysts were prepared by *in situ* generation of Au-NP within a PEG-grafted low-crosslinked polystyrene matrix as previously described.(3) The bioorthogonal [Au]-triggered release of Belinostat was investigated in culture with human lung cancer A549 cells. A549 cells were seeded in a 96 well plate (1,500 cells/well) and incubated for 48 h. Each well was then replaced with fresh media containing: [Au]-resins (1 mg/mL); **2a** (30 μM); Belinostat (30 μM) or a combination of [Au]-resins + **2a** (30 μM). After 5 d of treatment, cell viability was determined by PrestoBlue™.

Results Derivative **2a** mediated patently lower cytotoxicity than the parent drug, with a projected EC_{50} (**2a**) / EC_{50} (Belinostat) value far beyond two orders of magnitude. Derivative **2a** elicited a potent cytotoxic effect in cancer cell culture only in the presence of the Au-catalyst while complete innocuity in its absence. The observed antiproliferative effect was equivalent to that mediated by unmodified drug, unequivocal evidence that the active drug is released *in situ* by heterogenous gold chemistry.

Conclusion We have developed a completely inactive precursor of chemotherapeutic drug Belinostat and demostrated its Au-catalysed activation in cell culture.

References

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