Exploitation of the allosteric relationship between RAPTA T and Auranofin on the Nucleosome Core Particle in the design of novel anti-cancer agents.

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Dinuclear metal complexes have emerged as a promising class of biologically active molecules that display interesting anti-cancer activity and properties. As a consequence, both homo- and hetero-bimetallic combinations are being explored. An allosteric relationship between RAPTA-T, a ruthenium(II) anti-tumoral, and Auranofin, a gold(I) anti-rheumatic drug, is observed on nucleosome core particle (NCP). The binding of RAPTA-T to the surface of H2A-H2B dimer induces a kink in the long α-helix of the H2A histone protein that enables Auranofin to bind to two previously inaccessible sites. [1],[2] This allosteric relationship has been exploited to design and synthesize two generations of hetero-ruthenium(II)-gold(I) complexes. The design is based on crystallographic and computational data with the aim of simultaneously binding to the sites of the parent drugs, Auranofin and RAPTA-T, on the NCP. Here, we demonstrate that a single hetero-bimetallic ruthenium(II)-gold(I) complex can cause the same allosteric effect as the binding of mono-nuclear RAPTA-T and Auranofin.

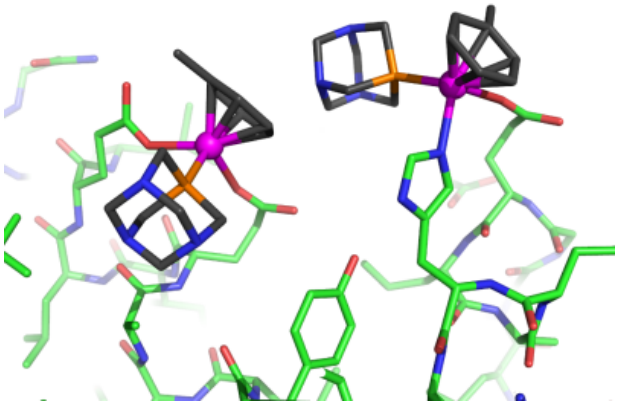

Figure 1. Binding sites of the RAPTA-T moiety on the histone component of the NCP.

[1] Z. Adhireksan, G. E. Davey, P. Campomanes, M. Groessl, C. M. Clavel, H. Yu, A. A. Nazarov, C. H. F. Yeo, W. H. Ang, P. Dröge, U. Rothlisberger, P. J. Dyson, C. A. Davey, *Nat. Commun.* **2014**, 5, 3462.
[2] Z. Adhireksan, G. Palermo, T. Riedel, Z. Ma, R. Muhammad, U. Rothlisberger, P. J. Dyson, C. A. Davey, *Nat. Commun.* **2017**, 8.