Tale of a successful failure: gold(III)-glycoconjugates as antiviral agents against SARS-CoV-2

A. Pettenuzzo,[a] M. Gil-Moles,[b] I. Ott,[b] L. Ronconi[a]*
[a] National University of Ireland Galway, School of Chemistry, University Road, Galway H91 TK33 (Ireland)
[b] Technische Universität Braunschweig, Institute of Medicinal and Pharmaceutical Chemistry, Beethovenstr. 55, Braunschweig 38106 (Germany)
luca.ronconi@nuigalway.ie

Rapidly dividing tumor cells require higher amounts of nutrients and energy for their abnormal proliferation, and glucose is no exception (the so-called "Warburg effect"). Consequently, such increased demand of glucose by cancer cells makes it very attractive to selectively target tumor sites. In particular, tailored glucose-like substrates can be conjugated to chemotherapeutics to attain the site-specific delivery of drugs into the affected tissues.[1]

In this context, we have previously developed some gold(III)-dithiocarbamato glycoconjugates of the type [$Au^{III}Br_2$(SSC-Inp-GlcN)] (Inp = isonipecotic moiety; GlcN = various amino-glucose substrates)[2] with a view to combining the antitumor properties and favorable toxicological profile of the gold(III)-dithiocarbamato scaffold previously reported,[3] along with an improved selectivity and cellular uptake provided by the coordinated glucose-containing carrier ligand, through the exploitation of the glucose-mediated cellular internalization provided by glucose transporters over-expressed in tumor cells.[4] Unfortunately, this class of complexes exhibited no cytotoxic activity *in vitro* towards a panel of human tumor cell lines, notwithstanding their high cell uptake and internalization.

On the other hand, such metal-glycoconjugates showed promises as antiviral agents against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Remarkably, they proved to induce 98-99% inhibition of SARS-CoV-2 Papain-like Protease (PL^{Pro}) activity (which plays a key role in virus replication), and to block completely virus replication in SARS-CoV-2-infected cells at the non-toxic (500 μM) concentration over 24 h.[5]

We here report on how an initial complete failure may have opened up new perspectives to the development of non-toxic metallodrugs capable of acting as potent inhibitors of specific SARS-CoV-2 target proteins.

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