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Together with taking an enormous human toll, cancer also has the greatest economic impact from premature death and disability, accounting for close to one trillion dollars from lost years of life and productivity (excluding direct medical costs) in 2008 [2]. Therefore, it is not surprising that the global health agenda is focusing on making an impact on cancer through the development and implementation of strategies to provide more effective prevention and treatment plans.

In this regard, according to the massive amount of papers in the literature reporting on the anticancer activity of a number of different substances, ranging from natural products to xenobiotics, it appears that killing cancer cells seems to be simple. However, doing this without affecting healthy tissues proved challenging so far. Consequently, anticancer drug development has shifted in recent times from traditional cytotoxic non-specific treatments towards rationally designed drugs targeting certain biomarkers or receptors overexpressed in tumors [3]. This would enable preferential killing of cancer cells with little toxicity towards healthy ones and lower administered doses.

The concept of selective delivery of drugs for curing diseases was first described by Ehrlich in 1906, known as the “magic bullet” strategy, which should have three distinctive characteristics: (i) an effective target of the disease, (ii) a drug to eradicate the diseased tissue, and (iii) a carrier to selectively deliver the drug to the target [4]. However, in order to design suitable drug delivery and targeting systems, it is important to initially recognize the biological differences between normal and cancer cells.

Since the oncogene revolution, extensive research has been focused on gene mutations and metabolic reprogramming to decipher the “hallmarks of cancer” [5]. The identification of many different signaling pathways, oncogenes, and tumor suppressor genes involved in carcinogenesis and tumor progression, have contributed greatly towards more selective chemotherapeutic drugs which target oncogenic molecules. However, malignant transformations stem from multiple genetic and epigenetic mutations which are continuously changing as the disease progresses, even within histopathologically identical.
tumors [6]. Therefore it is challenging to specifically target individual genes as it would require multiple targeting agents to fully eradicate tumor cells.

On the other hand, as cancer cells are fast-proliferating compared to healthy ones, they require increased levels nutrients/energy and, therefore, have developed alternative and/or modified metabolic processes to sustain higher growing rates. In particular, the difference lies in the stressful and complex tumor microenvironment where the concentration of crucial nutrients is not homogeneously spaced, thus leading to metabolic changes. Such abnormal alterations in the tumor metabolism can be then exploited showing advantages as a focus for targeted therapies.

This review paper aims to summarize progress in the development of anticancer chemotherapeutics designed to specifically target the glucose metabolism of tumors in order to attain the site-specific delivery of chemotherapeutics into the affected tissues. In particular, it will focus on recent advances in the conjugation of metal-based potential anticancer agents to glucose-like substrates as a suitable strategy to promote intracellular transfer and delivery of metallodrugs in tumors.

2 Metabolic reprogramming in tumors

2.1 Tumor hypoxia

Hypoxia (i.e. deprivation of adequate oxygen supply) is a major feature of most human cancers and results from the limited diffusion of oxygen in poorly vascularized tumors [7]. This condition may induce genome instability by generating reactive oxygen species (ROS) [8] and down-regulating DNA repair pathways [9], ultimately leading to apoptosis. Since tumor microvasculature promoted to partly respond to the effects of hypoxia is often insufficient to contrast such oxygen depletion [10], cancerous cells respond to this hypoxic environment by reprogramming their metabolism.

The major oxygen-responsive pathway affected by this metabolic adaptation involves transcription factors belonging to the hypoxia-inducible factor (HIF) family [11]. Hypoxia-inducible factor 1 (HIF-1) is an αβ-heterodimeric protein made up of two subunits, HIF-1α and HIF-1β. The former is not stable under normoxic conditions since, in presence of oxygen, it is hydrolyzed by prolylhydroxylases (PHDs) and is ultimately degraded by the proteasome [12]. On the other hand, a hypoxic environment does not favor the PHD-triggered inactivation of HIF-1α, which then binds to the HIF-1β subunit in the cell nucleus leading to the formation of the active form of HIF-1 which, eventually, promotes the transcription of a number of genes [13].

The large majority of human tumors, in particular the most aggressive ones, are known to overexpress HIF-1, thus inducing a broad adaptive response to hypoxia [14], including the promotion of genes involved in angiogenesis, the physiological process triggering the formation of new blood vessels from preexisting ones, such as vascular endothelial growth factor A (VEGFA) which supports the growth of new blood vessels [15].

Intriguingly, the most significant consequence of HIF-1 activation is the overexpression of several glycolysis-related genes inducing the abnormal promotion of the glycolytic flux [16].

2.2 Glucose metabolism in tumors

All cells require glucose for the generation of adenosine triphosphate (ATP) as energy source to drive a number of subsequent synthetic processes. Once internalized into the cell through transmembrane glucose transporters (GLUTs), one molecule of glucose undergoes a ten-step enzyme-catalyzed “demolition” process (termed glycolysis) devoted to its oxidation to pyruvate. The overall net result is the production of two molecules of pyruvate, two molecules of ATP and two molecules of reduced nicotinamide adenine dinucleotide (NADH) (Fig. 1) [17].

Typically, normal cells metabolize glucose under aerobic conditions and, as such, the glycolytic pathway is coupled to the mitochondrial oxidative phosphorylation (OXPHOS) process. Therefore, pyruvate produced via glycolysis enters mitochondria and is used to generate acetyl-coenzyme A (acetyl-CoA) which then enters the tricarboxylic acid (TCA) cycle. As a result, NADH is formed which is needed to maximize ATP production, and up to 36 molecules of ATP may be produced by 1 molecule of glucose. Alternatively, under anaerobic conditions, OXPHOS is unlikely to occur and pyruvate is converted to lactate which is excreted from the cell through the monocarboxylate transporter (MCT) to control intracellular pH levels (Fig. 1).

The compelling evidence for hypoxia in tumor tissues accounts for the altered glucose metabolism in cancer cells. In 1924, the German biochemist Otto Warburg first postulated “anaerobic” glycolysis as the major glucose metabolism in tumors, a phenomenon known as “the Warburg effect” [18]. In particular, he showed that pyruvate resulting from the anaerobic glycolytic process, favored by the hypoxic tumor intracellular environment,
is more likely converted to lactate rather than undergoing mitochondrial OXPHOS. Such high production of lactic acid is consistent with increased extracellular acidosis compared with normal cells [19]. Although the anaerobic glycolytic pathway is less efficient than OXPHOS in generating ATP (2 vs. 36 ATPs per glucose molecule), glycolysis itself produces ATP at faster rate [20]. This accounts for Warburg’s observation that tumor cells are generally characterized by exaggerated demand and consumption of glucose to sustain their abnormal proliferation rates [21, 22].

As previously stated, HIF-1 plays a key role in promoting glycolysis in hypoxic tumor cells, leading to the Warburg effect. Such metabolic reprogramming responds to the greater demand of energy and glycolysis-related anabolites, as well as to the decreased effectiveness of the overall glycolytic flux preferentially forming lactate. Specifically, HIF-1 promotes [16]:

- the overexpression of glucose transporters 1 and 3 (GLUT1 and GLUT3);
- enhanced transcription of hexokinases 1 and 2 (HK1, HK2), phosphofructokinases 1 and 2 (PFK1, PFK2), aldolases A...
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and C (ALDA, ALDC), phosphoglycerate kinase 1 (PGK1), enolase 1 (ENO1), pyruvate kinase M2 (PKM2);
- the expression of pyruvate dehydrogenase kinases 1 and 2 (PDK1, PDK2);
- enhanced production of monocarboxylate transporter 4 (MCT4).

Owing to the abnormal demand of glucose in tumor cells, the overexpression of GLUT1 and GLUT3 facilitates its uptake, whereas its conversion to pyruvate is favored by the enhanced transcription of the enzymes directly involved in the whole process (that is, HK1, HK2, PFK1, PFK2, ALDA, ALDC, PGK1, ENO1, PKM2). Furthermore, the expression of PDK1 and PDK2 inhibits pyruvate dehydrogenase (PDH) and, consequently, the conversion of pyruvate to acetyl-CoA, preventing its entry to the TCA cycle in mitochondria and to undergo the OXPHOS process. At the same time, the expression of lactate dehydrogenase 5 (LDH5) is promoted, thus favoring the conversion to lactate. Finally, the overexpression of MCT4 allows lactate to be effectively sent out of the cell.

3 Targeting tumor glycolysis in cancer chemotherapy

Owing to its role in promoting tumor glycolysis, HIF-1 is an attractive target in cancer chemotherapy. In particular, its low activity in normal tissues makes it potentially selective toward tumor cells with minimal side-effects [23-25]. In

Figure 2. Representative examples of drugs targeting tumor glycolysis currently undergoing clinical trials (alleged target(s) in brackets).
a broader way, all the effectors of tumor glycolysis, in particular those whose (over)expression is promoted by the activation of HIF-1, may be regarded as suitable targets for the development of anticancer agents. To date, a few potential anticancer agents aiming at counteracting tumor glycolysis have entered Phase I-III clinical trials (Figure 2), and many others are undergoing preclinical evaluation [26,27].

### 3.1 GLUTs inhibitors

Among all, a suitable strategy is based on the development of chemotherapeutics specifically targeting glucose transporters (GLUTs). GLUTs are devoted to the recognition and cellular internalization of glucose, subsequently entering the glycolytic flux to provide energy and nutrients for cell growth and sustenance. There are three identified classes of GLUTs based on their primary sequence and specific affinity for glucose or other carbohydrates [28]. GLUT1-GLUT4 belong to Class 1 and are selective for glucose transport, whereas Class 2 (GLUT5) and Class 3 (GLUT6, GLUT8, GLUT10) show preference for other sugars. Remarkably, all GLUTs consist of 12 transmembrane domains characterized by similar amino acid sequences and tertiary structures [29].

In order to support the abnormal proliferation rates, the activity of GLUTs in tumors is 10 to 12-fold higher than in normal tissues, thus indicating the strong dependence of cancer cells on such transporters for their survival and growth [29,30]. In particular, the activation of HIF-1 under hypoxic conditions induces the overexpression of GLUT1 and GLUT3 in a wide range of human tumors, thus providing cancers with the capability to take up and internalize glucose even when its supply is limited [31]. Accordingly, tumors penchant to upregulate glucose uptake and the association of the overexpression of GLUT1 and GLUT3 with poor prognosis of a number of human tumors have become in recent years hallmarks of cancer [32,33].

Such avidity of glucose by fast-proliferating cancer cells has been already exploited for the detection of primary tumors and metastases and their staging in clinics. In this regard, the positron emission tomography (PET) tracer $[^{18}F]$-fluorodeoxyglucose was developed as diagnostic probe owing to its increased preferential uptake in a number of tumors [34]. Nevertheless, from a therapeutic point of view, the overexpression of GLUTs in tumors provides the rationale to design GLUTs inhibitors capable of depleting cancer cells of a major nutrient by blocking glucose uptake, thus thwarting the glycolytic flux and, eventually, inducing cell death by “starvation”.

In this context, some natural products belonging to the family of flavonoids were found to exert anticancer activity by inhibiting GLUTs, the most promising being silybin [35] (Fig. 2) and phloretin [36] (Fig. 3). However, owing to the varied biological features of flavonoids, including the well-known antioxidant properties [37], it seems daring to assume that their anticancer effectiveness is only associated with their inhibitory effect on GLUTs.

On the contrary, direct inhibition of GLUTs was linked to the cytotoxic activity of glucose-like or glucose-mimicking agents (Fig. 3). For example, 6-glucose-chlorambucil, STF-31 and fasentin were shown to exert their anticancer activity by binding directly to GLUT1 (and also GLUT4 for the latter) leading to its inactivation [38-40]. Additionally, two $O$-protected derivatives of the pseudo-sugar myo-inositol proved cytotoxic toward cancer cells in vitro upon inhibition of GLUTs in a dose-dependent fashion [41], whereas dipyriramole, isobutylmethylxanthine and forskolin were reported to selectively inhibit GLUT4 activity [42].

Notwithstanding the potential of GLUTs inhibition as a suitable strategy to block tumor glycolysis, only a few substances have GLUTs inhibition undoubtedly identified as the primary anticancer mechanism of action.

### 3.2 Drug glycoconjugation as anticancer approach

An alternative approach is to target GLUTs not to inhibit them but to exploit their overexpression in tumors for the site-specific delivery of therapeutics. This is based on the conjugation of a therapeutic agent to glucose-like or glycomimetic substrates acting as carriers of a pharmaceutically-active core [43,44]. The rationale of such designing strategy relies on the assumption that the glucose-like scaffold (anchored to a bioactive molecule) should be recognized by GLUTs and the glycoconjugate internalized as a whole. Eventually, once taken up the cytotoxic species could exert its anticancer activity directly inside the tumor cell, thus acting as a “Trojan Horse”.

These glycoconjugates may be regarded as pro-drugs in which the structural features of the glucose-like scaffold conceal the attached active drug. Remarkably, they have the potential to combine the antitumor properties of the drug with an enhanced uptake and tumor selectivity provided by the glucose-like tail-mediated cell internalization upon exploitation of the GLUTs overexpressed in cancer cells, therefore increasing the therapeutic effectiveness without affecting healthy tissues.
A successful application of this targeting strategy has been reported for the glycoconjugate obtained by linking the nitric oxide releasing agent S-nitroso-N-acetylpenicillamine (SNAP) to the C(2) position of a glucose molecule generating 2-glucose-SNAP (Fig. 3). Remarkably, it was observed that the conjugate had up to 5000-fold higher cytotoxicity toward ovarian carcinomas in vitro compared with the non-conjugated SNAP precursor, and such impressive enhanced activity was linked to the capability of 2-glucose-SNAP to target GLUT1 [45]. Similar outcomes were reported also for the glycoconjugate of the nitrogen mustard alkylating agents ifosfamide and glufosfamide (Fig. 3), for which enhancement in anticancer activity upon conjugation was assessed in tumor cells overexpressing GLUTs [46]. Remarkably, in both cases, no evidence of GLUT inhibition was observed.

Starting from this proof-of-concept, the field of glycoconjugation has accelerated since [47], although involving almost exclusively non-metal-containing species.

### 3.3 Why metal-based glycoconjugates?

Modern medicinal chemistry and drug design have been showing ever-increasing interest in the development of metallo-drugs with well-defined pharmacological profiles. Starting from the accidental discovery of the therapeutic effectiveness of cisplatin in the mid-1960s, research has been generating an impressive number of both platinum- and other metal-based anticancer agents [48-50]. Unfortunately, poor bioavailability, water
solubility and stability under physiological conditions, along with lack of tumor selectivity and overall toxicity of the metal derivatives proved detrimental. Consequently, only a small bunch of platinum(II) complexes were granted clinical approval and marketed globally [51]. Nevertheless, metal centers in different oxidation states possess peculiar biological properties, coordination modes and kinetic behavior that can interfere with cellular processes in tumors, such as cell division and carcinogenic reactions, through mechanisms hardly related to organic drugs.

Owing to the attractiveness and potentiality of metallo-drugs, latest approaches focus on complexes with biologically-active ligands having tumor targeting properties, thereby maximizing the impact on cancer cells and minimizing the occurrence of adverse side-effects [52,53]. Conjugated drugs incorporating a tumor targeting group (carrier) and a cytotoxic metal-containing “smart bomb” have been emerging as promising approaches for targeted anticancer chemotherapy [54]. In this context, carbohydrate-metal conjugation could be expected to show favorable biological and physiochemical properties including biocompatibility, enhanced water solubility, enantiomeric purity, increased stability of the metal core, and reduced or no toxicity. Most importantly, tumor selectivity can be achieved through the coordinated carbohydrate ligands exploiting upregulated signaling pathways and/or certain glycolytic enzymes within the altered cancer cell metabolism [55].

Simple carbohydrates are commercially available and relatively inexpensive substrates with the potential to bind many different transition metals and, as such, have attracted increasing attention in recent years [56-58]. In particular, much effort has been focused on glucose-functionalized metal complexes specifically designed to be recognized by GLUTs and potentially delivered inside the tumor cell, provided that such glyco-metal conjugates still follow the same metabolic pathway of the carrier molecule (i.e. the glucose-like targeting tail). In fact, a major drawback of this approach may be the affection of the transport properties of the carrier upon conjugation, therefore limiting the anticancer potential of the conjugate itself. For instance, it was suggested that the presence of the free anomic group is necessary for the recognition of the glucose-like moiety by GLUTs, and that accessibility to the glucose unit by GLUTs is strongly dependent on where the metal-containing scaffold is bound to the carbohydrate ligand [26].

Although from a synthetic point of view the coordination of glucose-like substrates to metal centers can be somewhat tricky, some glyco-metal conjugates have been developed and their cytotoxic activity reported, but their mechanism of action is still unclear. Advances in the functionalization of metal complexes with carbohydrate ligands are summarized and discussed in the following sections. Cyclodextrin derivatives, non-covalent interactions, nanoparticles, polymers and macromolecular aggregates go beyond the scope of this review and will not be covered.

4 Metal-based glycoconjugates

4.1 Platinum

Clinically-established platinum drugs cisplatin, carboplatin, oxaliplatin (worldwide), nedaplatin (Japan), lobaplatin (China) and heptaplatin (South Korea) are amongst the most widely used drugs for the treatment of cancer, although therapeutic success is hindered by some severe side-effects, as well as by tumor resistance (either intrinsic or acquired during cycles of therapy) [59]. Therefore, much effort has been made to mitigate drawbacks, in particular through the functionalization of non-leaving ligands with a carrier moiety in order to tune their pharmacological profile by generating tumor selective, less toxic metallo-drugs and improving some properties such as water solubility and cellular uptake [60].

In this regard, different backbones were proposed to glyco-platinum conjugation either via direct binding to the metal center or by coordinating a chelating ligand linked to a carbohydrate scaffold through a spacer [61,62].

4.1.1 Amino-sugar derivatives

In the attempt to improve cisplatin solubility in water, a number of amino-sugars were directly coordinated to the metal center (Fig. 4).

Tsukomura et al. reported on the synthesis of a series of platinum(II) glycoconjugates of diaminocarbohydrates [63]. Complexes were tested in vivo toward murine S180 sarcoma and Pt-1(Cl) showed anticancer activity comparable to cisplatin, although accompanied by much lower acute toxicity (LD₅₀ 50 mg kg⁻¹ vs. 13 mg kg⁻¹). On the contrary, it proved inactive against murine L1210 leukemia, whereas in this case Pt-2 turned out to be the best performer in terms of tumor remission.

Keppler and co-workers evaluated the cytotoxic activity of some structural analogues of Pt-1(Cl) obtained by replacing chlorides with iodo (Pt-1(I)), oxalato (Pt-1(oxalato)) and malonato (Pt-1(malonato)) ligands.
Although all exhibited IC\textsubscript{50} values \textit{in vitro} lower than carboplatin toward human HeLa cervical adenocarcinoma and SW480 colorectal adenocarcinoma cell lines, Pt-1(Cl) still showed the higher activity. As expected, the reactivity toward the model nucleotide deoxyguanosine monophosphate (dGMP) was shown to decrease according to the order dichlorido > diiodido > oxalato > malonato (consistent with the corresponding aquation rates), but no clear correlation between binding affinity to dGMP and cytotoxicity was observed. This suggested that additional factors other than activation by hydrolysis had to be involved (e.g. different cellular uptake).
Hanessian and Wang reported on cisplatin analogues derivatized with diamino-dihydroxypropyran (Pt-3(H) and Pt-4) or 3-diaminomethoxypropyram ligands (Pt-3(Me)) [65]. Although less potent than oxaliplatin, the former showed cytotoxic activity comparable to cisplatin against murine L1210 leukemia and P388 lymphoma both in vitro and in vivo. Interestingly, the methylated counterpart, Pt-3(Me), proved much less active, probably due to the decreased water solubility upon methylation. Overall reduced activity was observed also when the chlorido ligands were replaced by the chelating cyclobutane-1,1-dicarboxylate (Pt-5), owing to its slower aquation kinetics.

The cationic platinum(II) complex [PtCl(methyl-3,4-diamino-2,3,4,6-tetrahydro-α-L-lyxopyranoside)(DMSO)] NO₃ (Pt-6) was reported to exert in vitro cytotoxicity levels similar to cisplatin against murine L1210 leukemia cells [66]. Intriguingly, notwithstanding the lower water solubility, the corresponding neutral analogue Pt-7 was found equally active not only in murine L1210 leukemia cells but also toward two different murine L5178Y-S and L5178Y-R lymphoma cell lines differing in their double-strand breaks and nucleotide excision repair ability [67,68].

Along with mononuclear complexes, some polynuclear platinum glycoconjugates were prepared and their antiproliferative properties evaluated. For instance, the water soluble di- (Pt-8) and trinuclear (Pt-9(X)) complexes, bearing a disaccharide moiety of sucrose, were obtained showing in vitro and in vivo anticancer activity against murine Lewis lung carcinomas. Remarkably, the mononuclear counterparts (Pt-10(X)) proved inactive [69].

Anthracyclines, especially doxorubicin, are a class of glycoconjugates used in the treatment of a broad spectrum of malignancies, although severe side-effects, such as myocardiopathy and congestive heart failure arising upon continuous administration, have limited their clinical use [70]. In the attempt to combine the anticancer activity of doxorubicin and cisplatin, the former was bound to a cisplatin-like scaffold through its amino-sugar moiety (Pt-11). Unfortunately, the overall anticancer activity proved only comparable to that exerted by the individual drugs [71].

### 4.1.2 Glyco-appended derivatives

The use of spacers linking anticancer metal-based scaffolds to carbohydrates can be useful to tune the physicochemical and pharmacological properties of the glyco-metal conjugates without affecting the cytotoxic activity of the metal core. Linkers may include chelating diamino, carboxylato, dicarboxylato and P-donor ligands (Fig. 5).

Cisplatin analogues bearing a monosaccharide moiety connected through a 2-hydroxy-1,3-diaminopropano (Pt-12) or 3-hydroxy-1,2-diaminopropano (Pt-13) spacers were synthesized by Chen and co-workers [72,73]. The effectiveness in vitro was investigated for the β-d-glucose derivative, showing promise against human A2780 ovarian carcinoma and MeWo melanoma cell lines, although no appreciable cytotoxicity was observed in the corresponding cisplatin-resistant parent cells. Subsequent introduction of alternative monosaccharides, such as d-mannose, d-galactose and l-glucose, allowed some structure-activity relationship considerations to be formulated. For example, complexes containing α- anomers were overall more active than the corresponding β-anomers, whereas no difference was observed between l and d isomers. Among all, the α-d-mannose derivative showed the greater anticancer potency, supporting the hypothesis of a preferential uptake of the mannose moiety into the tumor cells.

Simple monosaccharides derivatized with a carboxylic function, such as gluconic, glucuronic and galacturonic acid, were coordinated to cisplatin-like substrates and evaluated for anticancer activity in vitro and in vivo, but outcomes were below expectations [74]. On the contrary, functionalization of the malonato ligand of carboplatin provided insights into the mode of action of this class of glyco-platinum conjugates.

Complex Pt-14 was shown to be more potent than carboplatin toward a panel of human tumor cell lines in vitro [75]. Subsequent in vivo studies confirmed its capability to suppress tumor growth in human HT29 colorectal adenocarcinoma-bearing xenografts, together with a dramatic increase of the maximum tolerated dose compared with carboplatin itself. Remarkably, its anticancer activity was blocked in presence of GLUT inhibitors, supporting the involvement of GLUTs in the mechanism of action.

An interesting study carried out by Reedijk and co-workers involved the design of compound Pt-15, in order to generate a glycoconjugate capable of entering tumor cells through GLUTs and, once taken up, undergoing β-glucuronidase enzymatic cleavage, thus releasing the carboplatin-like species directly into the tumor site [76]. This pro-drug approach was confirmed by means of NMR studies, but further biological data have not been provided yet.

Moker et al. reported on a number of similar carboplatin glycoconjugates in which the malonato ligand was linked to a glucose molecule at the unusual C(3)
position through an alkyl spacer (Pt-16), but no significant improvements in terms of cytotoxic activity were recorded (compared with carboplatin) [77-79].

Finally, it is worth highlighting a recent report from Liu and co-workers, whose platinum glycoconjugate Pt-17(X) not only proved more cytotoxic than carboplatin, but its antiproliferative activity was completely blocked in presence of the GLUT inhibitor phlorizin, suggesting the involvement of GLUT-mediated uptake in cell internalization [80].

In order to circumvent the development of tumor resistance upon treatment with platinum drugs, Shi and co-workers designed a series of platinum(II) glycoconjugates functionalized with diphenylphosphine (Pt-18) [81,82]. The rationale of such designing strategy relies on the attempt to exploit a pH-dependent ring-opening and ring-closing mechanism provided by the hemilabile O,P-donor ligands. In fact, the labile oxygen-platinum bond would be cleaved in the acidic tumor environment, thus promoting the generation of a free coordination site with potential to interact with cellular DNA. Additionally, the bulkiness of the glucose-like scaffold would prevent the undesirable reaction of the platinum center with other biomolecules (mainly sulfur-containing), so as to reduce side-effects. Pt-18 proved active in particular against murine P388 lymphoma cells (IC_{50} = 100 nM), but further details on its mode of action were not disclosed.

Figure 5. Platinum derivatives of glyco-functionalized ligands.
4.1.3 Glyco-organometallic derivatives

Owing to advances in the development of organometallic anticancer agents [83], some glyco-functionalized organoplatinum derivatives have been reported, although cytotoxic activity rarely exceeded that of the reference drug cisplatin. Nevertheless, following the encouraging results obtained for terpyridine-platinum(II) complexes [84], the cationic water-soluble fluorescent compound Pt-19 (bearing a glycosylated arylacetylide ligand) was generated, showing IC$_{50}$ values in the nanomolar range (0.06 - 0.2 µM) toward several human tumor cell lines. Remarkably, it proved up to 100-fold more active than cisplatin and 8-fold more cytotoxic than the corresponding non-glycosylated analogue [85]. Subsequent in-depth mechanistic studies revealed a strong interaction with ctDNA through a non-intercalating binding mode and the capability to induce preferential apoptosis rather than necrosis [86].

4.2 Palladium

Owing to its chemical properties and coordination modes similar to platinum(II), palladium(II) has attracted great interest in terms of anticancer potential [87]. Both metals in the +2 oxidation state generate square-planar complexes and are soft Lewis acids forming preferentially bonds with N- and S-donors. On the other hand, palladium(II) derivatives are thermodynamically and kinetically less
stable than the platinum(II) counterparts, and undergo aquation and ligand exchange much faster [88], thus limiting their medicinal applications [89]. Therefore, an appropriate design of the ligands, including the development of glycoconjugates, would allow the tuning of hydrolysis rates (Fig. 6).

The first glyco-functionalized palladium(II) derivatives reported in the literature (Pd-1) resembled the glyco-appended platinum(II) counterparts Pt-12 (Fig. 5), in which a carbohydrate moiety is anchored to the metal center through a 2-hydroxy-1,3-diaminopropano linker [90]. A number of α-saccharides were used, including α- and β-anomers of glucose, galactose, mannose, xylose and maltose, but only the maltose analogue was shown to exert some cytotoxic activity.

Kumar et al. reported on palladium(II)-carbohydrate derivatives in which a variously substituted 1,2-O-isopropylidene-xylofuranose moiety is anchored to a metal-chelating pyridyltriazole ligand (Pd-2) [91,92]. Among all, the OH- and ferrocenyl-substituted complexes exerted the highest antiproliferative activity against a panel of human tumor cell lines, with IC_{50} values in the range 10-20 µM. Interestingly, replacement of the xylofuranose scaffold with variously substituted glucose moieties totally inhibited the overall cytotoxic activity [93]. On the other hand, linking a glucose molecule to a modified amino-pyridine led to a palladium(II) complex (Pd-3) showing in vitro and in vivo anticancer activity greater than the platinum(II) analogue toward gastric cancer, and the capability to overcome cross-resistance to cisplatin in the cisplatin-resistant gastric cancer cells [94].

Palladium(II) derivatives of glyco-functionalized porphyrins have been developed as potential photosensitizers in photodynamic therapy (PDT) [95]. In particular, S-glycoconjugated porphyrin and pyrrolidine-fused chlorin coordinated to the metal center (Pd-4 and Pd-5, respectively) were designed on purpose to combine the phototoxicity of the palladium(II)-based photosensitizer with an increased cellular uptake into tumor cells provided by the glucose-like moieties [96]. Interestingly, glucose functionalization proved effective to enhance cellular uptake (up to 4-fold higher than non-glycosylated analogues). Non-acetylated derivatives showed photocytotoxicity only, whereas acetylated ones and platinum(II) counterparts did not exert any antiproliferative activity either in the dark or upon irradiation [97,98]. Nevertheless, IC_{50} values were only comparable to, or even slightly higher than, non-glycosylated metal-free and metal-containing photosensitizers, so further evaluations were discontinued.

4.3 Gold

Among non-platinum anticancer agents, gold derivatives are currently gaining ground as a new class of potential chemotherapeutics owing to their capability to inhibit tumor cell growth through non-cisplatin-like mechanisms of action [99,100]. Gold complexes with reported antiproliferative properties include different ligands bound to the metal center in either +1 or +3 oxidation states.

Gold(III) shares some important chemical features with platinum(II), such as the typical square-planar coordination geometry and the same d^8 electronic configuration, thus making it very attractive for the development of alternative antineoplastic drugs [101].

![Figure 7. Clinically-established gold-based antiarthritic drugs.](image-url)
On the other hand, the only gold derivatives that have been marketed to date are a few gold(I)-based drugs, traditionally for the treatment of rheumatoid arthritis (Fig. 7) [102]. Intriguingly, two of them (namely, solganal and auranofin) contain a glucose-like scaffold directly bound to the gold(I) center.

4.3.1 Auranofin and its analogues

Together with its antiinflammatory activity, the complex [(2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S)](triethylphosphino)gold(I) (auranofin) showed promising anticancer activity in vitro and, as such, was extensively studied [103]. In fact, it proved cytotoxic toward several human tumor cell lines, including cisplatin-sensitive and -resistant ovarian cells [104], multiple myeloma [105] and leukemia [106] cells. Unfortunately, antitumor activity was confirmed in vivo only against murine P388 lymphoma [107,108]. Auranofin is currently undergoing Phase II clinical trials for the treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma and prolymphocytic lymphoma [109].

As to its mechanism of action, the antiarthritic activity seems to arise from the inhibition of enzymes such as cyclooxygenases [103], whereas the inactivation of the seleno-enzyme thioredoxin reductase is likely to account for its anticancer properties [104]. Nevertheless, the actual mechanism of transport and cellular internalization of auranofin is still unclear. Auranofin radiolabeled at the triethylphosphine (Ph) and thio-glucose (14C) moieties was used to investigate its cellular uptake [107,110,111]. The first two were detected in cell membrane, cytoplasm and nuclear fractions, whereas the latter was not. In particular, for cells exposed to IC50 concentrations of auranofin the amount of gold was over 100-fold higher in the intracellular rather than extracellular extracts. These findings suggested that sulphydryl groups on cell surface would bind the metal core by displacing the thio-glucose ligand, subsequently promoting the transport of the gold-triethylphosphine scaffold inside the cell and its distribution amongst membrane, cytosol and nucleus.

With the goal of improving the pharmacological profile of auranofin and reducing its toxicity, a number of analogues have been reported to date (Fig. 8). Replacement of the triethylphosphine ligand with other phosphines, phosphinites or amidophosphites (Au-1(X)) did not significantly modify the anticancer activity (compared to auranofin) in particular in vivo, neither did the use of glucose (either α or β), galactose or xylose instead of the tetraacetyl-thioglucose moiety [112]. Replacement of the coordinated phosphine with 1,3,5-triaza-7-phosphaadamantane (PTA, Au-2) or 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DAPTA, Au-3) increased the overall uptake in both human cisplatin-sensitive A2780 and -resistant A2780-R ovarian adenocarcinoma cells compared to auranofin, but this did not result in enhanced antiproliferative potency, suggesting the involvement of alternative uptake mechanisms [113].

An alternative glycoconjugation strategy was suggested by Shi and co-workers, in which glucose-like substrates were functionalized with a [PPh2] moiety at the C(3) position (Au-4) [114]. Notwithstanding the promising anticancer activity recorded in murine leukemia cells, further investigations were not reported.

Later on, a thio-sugar phosphole gold(I) derivative (Au-5) was reported to show increased stability under physiological conditions, water solubility, bioavailability and antiproliferative activity compared with the non-glycosylated counterpart [115]. Moreover, it proved more cytotoxic than auranofin toward human MCF7 breast adenocarcinoma, NCH89 and NCH82 glioblastoma, and murine C6 glioma cell lines with IC50 values in the low micromolar range. Subsequent biological studies demonstrated that Au-5 induces a dose-dependent arrest of the G2/M phase of the cell cycle and, contrary to what was previously hypothesized, the thioredoxin system was ruled out as potential target [116].

Advances in the field have led to the development of heterobimetallic complexes aimed at combining the anticancer properties of auranofin and platinum(II)-containing scaffolds. In this context, the gold(I)-thioglucose and {PtCl2} moieties were linked through a P,N,N'-spacer affording compound Au-6 [117]. The latter proved more cytotoxic in vitro than the individual auranofin and cisplatin, in particular when tested on cisplatin-resistant cell lines, although lack of tumor selectivity was a major drawback. Moreover, negligible interaction with DNA was observed, suggesting that biological targets would be determined by the gold center rather than platinum.

4.3.2 Carbene glycoconjugates

N-heterocyclic (NHC) carbene gold(I) complexes have been gaining interest for their potential in cancer chemotherapy due to their stability under physiological-like conditions and functionalization opportunities to tune their properties [118]. These include auranofin analogues in which the phosphine is replaced by carbene ligands [119].
NHC-carbene derivatives of tetraacetyl-thio-glucose-gold(I) (Au-7) exhibited cell growth inhibition in the micromolar range against human MCF7 and MDA-MB-231 breast adenocarcinoma, and HT29 colon adenocarcinoma cells in vitro, performing substantially better than the clinically-established drugs cisplatin and 5-fluorouracil [118,120]. Distribution studies revealed that most of the gold-containing species accumulate in the cell nucleus, although the involvement of thioredoxin reductase, estrogen receptors and cyclooxygenases is currently under evaluation [120,121].

Hackenberg et al. reported on the anticancer activity of NHC-carbene analogues of auranofin in which the alkyl substituents on the carbene were specifically modified (Au-8) [122]. Cytotoxicity studies were encouraging especially in human MCF7 breast adenocarcinoma and Caki-1 skin carcinoma cells, in particular in comparison to analogues where either the carbene or the thioglucose ligands are replaced by chlorides. On the contrary, variation of the alkyl chains did not substantially affect the anticancer activity.
4.4 Ruthenium

Among the non-platinum anticancer drugs, ruthenium complexes are the most widely investigated because of their peculiar cytotoxic and antimetastatic properties (Fig. 9) [123]. Two ruthenium(III) derivatives, namely trans-\([\text{RuCl}_4(\text{Im})(\text{DMSO})]_{\text{ImH}}\) (NAMI-A) and trans-\([\text{RuCl}_4(\text{Ind})_2]_{\text{IndH}}\) (KP1019), are currently undergoing Phase I and Phase II clinical trials, respectively. Cell internalization of these complexes seems to be mediated by transferrin, a protein normally devoted to the transport of iron into the cytoplasm. In fact, the high binding affinity of ruthenium(III) toward transferrin suggests an iron-mimicking mechanism promoting their uptake owing to the upregulated activity of transferrin into tumor cells. Once taken up, ruthenium(III) derivatives are commonly believed to exert their anticancer activity through the so-called “activation by reduction” mode of action, according to which the highly acidic and reducing tumor environment reduces the metal center to the +2 oxidation state, that is, the actual active species [124].

Consequently, much effort has been recently focusing on organoruthenium(II) complexes [125], including piano-stool-type derivatives such as RM175 [126] and RAPTA-C [127]. Remarkably, the amphiphilic character provided by the hydrophobic arene ligand and the hydrophilicity of the metal center, makes the ruthenium(II)-arene scaffold an excellent substrate to be coupled to different organic fragments to tune the overall pharmacological, including the conjugation to carbohydrates.

Keppler et al. replaced the PTA ligand with phosphite-carbohydrate ligands, generating a series of ruthenium(II) half-sandwich complexes (\(\text{Ru-1 to Ru-4}\), Fig. 10) [128,129]. The introduction of a sugar-based moiety would have improved water solubility along with providing selective targeting of, and enhanced uptake in, cancer cells. Such

![Image of ruthenium complexes](image_url)

**Figure 9.** Ruthenium-based anticancer drugs currently undergoing preclinical and clinical trials.
Metal-based glycoconjugates and their potential in targeted anticancer chemotherapy

Complexes showed moderate growth inhibition capability in vitro toward several human tumor cell lines. On the other hand, similar IC_{50} values were observed on cisplatin-sensitive and -resistant parent cell pairs (e.g. A2780 and A2780-R), thus accounting for the lack of cross-resistance with the reference platinum drug. Additionally, they proved selective toward cancer cells, compared to non-tumor endothelial cells, but no further biological evaluations (e.g. cell uptake) were reported.

Owing to the discovery of the in vitro cytotoxic properties of some Ru(0) clusters [130], a number of trinuclear ruthenium(0)-carbonyl derivatives of bicyclopentaphosphito-glucofuranoside (Ru-5) were synthesized and tested [131]. Overall, such clusters showed strong antiproliferative activity against several cancer cell lines, with IC_{50} values ranging from 0.1 to 0.8 µM. Cellular uptake and cytotoxicity proved to increase with lipophilicity, and evidence for antiangiogenic activity in vivo induced by arresting cell cycle in the G1/G0 phase was reported.

Owing to its involvement in a number of cellular processes, most of which have been uncovered during the last 10–15 years, RNA has been emerging as a potential target in the design of therapeutic and diagnostic agents [132]. Abnormal expression of microRNAs has been recently associated with the pathogenesis of human
cancer [133,134], thus making these non-coding portions of RNA attractive for the development of novel anticancer strategies, in particular by targeting RNAs with small molecules [135]. In this regard, aminoglycoside antibiotics (e.g. neomycin, paromomycin, kanamycin A) have shown high selectivity and affinity toward RNA structures and proved effective in modulating RNA functions [136,137].

In the attempt to combine the potential RNA-targeting properties of aminoglycosides with the anticancer activity of ruthenium(II)-arene scaffolds, guanidinylated neomycin-ruthenium conjugates were prepared [138]. In particular, compound Ru-6 showed significant anticancer activity in vitro toward human MCF7 breast adenocarcinoma and DU145 prostate carcinoma cells (IC₅₀ = 11.33 and 7.17 µM, respectively), and increased cellular uptake upon guanidylation (compared to the non-guanidinylated metal analogue). On the other hand, tumor selectivity was not accomplished and intracellular accumulation was reduced in comparison with the non-glyco-functionalized ruthenium(II)-arene derivative (ascribed to the overall decreased lipophilicity induced by the highly hydrophilic glycoside moiety).

4.5 Other metals

4.5.1 Copper

The development of copper derivatives with anticancer activity relies on the fact that the altered tumor metabolism induces different responses to this endogenous metal ion by cancer cells compared to normal ones. Its well-known redox activity and competitive affinity for enzyme binding sites occupied by other metals make the pharmacological exploitation of copper-based derivatives rather challenging and can induce toxic side-effects [139].

A few examples of glyco-functionalized mononuclear [140-142] and dinuclear [142] copper(II) derivatives have been reported but, apart from some routine in vitro cytotoxicity tests (although somewhat promising), no further studies aimed at elucidating their mechanism of cellular uptake and mode of action have been carried out to date.

4.5.2 Cobalt

In an attempt at combining the pharmacological properties of the well-established drug auranofin (Section 4.3.1) with the cytostatic activity of propargylhexacarbonyldicobalt (Co-AAS) [143], Ott et al. investigated the biological properties of some hexacarbonyldicobalt(0) complexes functionalized with fructopyranosyl alkyno ligands [144].

Overall, such compounds showed only moderate (IC₅₀ > 20 µM) cytotoxic activity in human MCF7 breast adenocarcinoma cells, compared with auranofin, Co-AAS and cisplatin activity (1.1, 1.4 and 2.0 µM, respectively). Interestingly, a correlation between lipophilicity and cytotoxicity was observed, since complexes bearing isopropylidene-protected fructopyranosyl moieties proved more active owing to their increased cellular uptake (as demonstrated by atomic absorption studies).

4.5.3 Tin

Organotin derivatives have been showing potential as alternative metallopharmaceuticals exhibiting anticancer activity in vitro against a number of human tumor cell lines [145], and as antimicrobial, antiinflammatory, cardiovascular, trypanocidal, antitumor, and antituberculosis agents [146].

The development of glycosylated tin(IV)-based anticancer agents has been recently reviewed (Fig. 11) [147]. For instance, Tabassum and co-workers designed octahedral dimethyltin(IV) derivatives linked to α-glucose (Sn-1) or α-maltose (Sn-2) through an ethanolamine spacer [148]. Notwithstanding the moderate antiproliferative activity in vitro towards human HuH7 hepatocarcinoma cells (IC₅₀ 30-35 µM), both complexes were shown to be potent inhibitors of topoisomerase I and to express specific regulatory genes (MMP-2 and TGF-β). Additionally, significant tumor regression was observed in in vivo models, especially for the monosaccharide analogue Sn-1.

Along this line, a number of glyco-tin(IV) conjugates have been obtained and tested for their anticancer activity [149]. Among all, the tetrahedral triphenyltin(IV) derivative Sn-3 was designed in such a way to tune the lipophilic/hydrophilic properties of the final product [150,151]. Mechanistic studies demonstrated its capability to induce apoptosis through a p53-dependent pathway involving proteins of Bcl-2 family, cytochrome-c and activation of caspase-3. Furthermore, inhibition of tumor growth in vivo was reported at a tolerable dose without affecting the normal physiological functions of the tested animals.

Finally, glyco-functionalized heterobimetallic complexes containing dimethyltin(IV) scaffolds and copper(II) or nickel(II) metal centers were recently synthesized and evaluated for their cytotoxicity in vitro [152,153]. Although promising GI₅₀ values (< 10 mg mL⁻¹) were obtained in human Colo205 colon carcinoma and MCF7 breast adenocarcinoma cells, further detailed mechanistic studies have not been reported to date.
Metal-based glycoconjugates and their potential in targeted anticancer chemotherapy

4.5.4 Metallocenes

Since the discovery in the late 1970s of the antitumor properties of titanocene dichloride, [Ti\textsuperscript{IV}Cl\textsubscript{2}Cp\textsubscript{2}] (Cp: cyclopentadienyl) (Ti-1, Fig. 12), metallocene derivatives have attracted much attention as potential metallodrugs. In fact, the promising pharmacological profile in colon, breast and lung cancers, allowed [Ti\textsuperscript{IV}Cl\textsubscript{2}Cp\textsubscript{2}] to be the first non-platinum anticancer drug to enter Phase II clinical trials. However, outcomes were not that promising compared to other treatment regimes, and further clinical trials were disregarded [154]. Nevertheless, titanocene dichloride had already opened up the way, and research in the field of metallocenes has been renewed over the last two decades, focusing on the functionalization of the cyclopentadienyl ligand(s) to achieve target specificity [155].

A series of titanocene derivatives with one (Ti-2) or both (Ti-3) cyclopentadienyl ligands functionalized with a ribofuranoside pendant have been synthesized and tested for in vitro cytotoxic activity toward a number of human tumor cell lines [156]. Among all, Ti-3 turned out to be the best performer, with activity comparable to cisplatin in human KB3.1 cervix carcinoma and murine L929 aneuploid fibrosarcoma cells.

Subsequent modifications included the replacement of chlorides with fluorides, leading to IC\textsubscript{50} values in the low micromolar range [157]. In particular, complex Ti-4 was reported to exert antiproliferative activity against human A2780 ovarian carcinoma cells 5-fold higher than cisplatin, as well as a remarkable 40% increase of cytotoxicity toward the corresponding cisplatin-resistant parent cell line (A2780-R) compared to the reference platinum drug.

Owing to the structural similarity with titanocene, molybdocene analogues of the type [Mo\textsuperscript{IV}Cp\textsubscript{2}L\textsubscript{2}] (L = 1-thio-\textbeta-d-glucose (Mo-1), 1-thio-2,3,4,5-tetraacetyl-\textbeta-d-glucose (Mo-2)) have been also investigated [158], but the overall poor in vitro cytotoxic activity did not warrant further biological studies.

Among all metallocenes, ferrocene (Fe-1) has been the most studied owing to its stability and versatility of...
functionalization of the two cyclopentadienyl ligands [159]. Ferrocene derivatives with potential medicinal applications include: (i) ferrocenium-based salts, (ii) functionalized ferrocenes, (iii) heteropolymetallic compounds (containing two or more metal centers and incorporating ferrocene ancillary scaffolds), and (iv) supramolecular architectures acting as carrier systems associated with cytotoxic ferrocenes.

Functionalization of ferrocene with carbohydrates has been widely reported in the literature. The first investigation on this class of compounds in terms of pharmacological potential dates back to 2000, when Itoh and co-workers developed some mono- and di-ferrocenyl derivatives conjugated to various sugar moieties [160]. In particular, compound Fe-2 proved promising as both an antimalarial and cytotoxic agent, with IC50 values in the low micromolar range.

A series of ferrocene analogues, in which one cyclopentadienyl ligands was linked to different pentose or hexose moieties through an amide (Fe-3) or a triazole (Fe-4)

![Figure 12. Glyco-functionalized metallocene derivatives.](image-url)
spacer, were described recently by Trivedi et al. [161,162]. Overall, such compounds exhibited high stability under physiological conditions and reasonable cytotoxic activity (IC\textsubscript{50} = 6−55 µM) towards murine Nuro2A neuroblastoma and human HeLa cervical adenocarcinoma, MDA-MB-231 breast adenocarcinoma, A549 lung adenocarcinoma and MCF7 breast adenocarcinoma cell lines, although lower than cisplatin.

Improved cytotoxicity was achieved by playing around with the spacer. In this regard, substitution of the amide/triazole linker with the longer and more flexible (p-hydroxyphenyl)chalcone (Fe-5) has led to a substantial increase of cell growth inhibition in human HL60 promyelocytic leukemia cells (IC\textsubscript{50} ca. 4 µM) but still only comparable to the non-glycosylated ferrocenylchalcone precursor (IC\textsubscript{50} = 2 µM) [163]. Finally, compounds like Fe-6 have been developed by Kepller and co-workers but, again, antiproliferative activity in vitro was not as satisfactory as expected and, thus, additional evaluations were not carried out [164].

### 4.5.5 Technetium and rhenium

Within the field of medicinal inorganic chemistry, metal-based radiopharmaceuticals play an important role as both diagnostic and therapeutic tools [165]. Among all, technetium-99m derivatives are currently the most employed in diagnostic medicine, with a total of 67 imaging agents approved over the years by the U.S. Food and Drug Administration and 17 currently marketed [166].

In this context, the conjugation of carbohydrates to technetium-99m-containing scaffolds can be used to influence uptake, accumulation and localization of the radionuclide in the tumor site. Schibli and co-workers generated a series of technetium-99m (and the corresponding “cold” rhenium-based analogues) tricarbonyl complexes bearing different tridentate chelating moieties (including iminodiacetate, N-(2-pyridylmethyl)glycine and N-aliphatic-tethered histidine) bound to glucose at the C(1), C(2), C(3) and C(6) position [162,168]. All complexes showed high stability in vitro but cellular uptake proved rather low and not mediated by a GLUT1-dependent process. On the other hand, this study showed that only complexes carrying C(2)-functionalized glucose pendants were able to induce an effective inhibition of hexokinases (paragraph 2.2). Additional docking experiments suggested that the functionalization of glucose (as well as monosaccharides in general) at the C(2) position would be the best “tolerated” for connecting metal scaffolds, so as to allow the carbohydrate to follow its usual metabolic pathway.

Along the same line, Orvig et al. developed a number of glucosamine derivatives functionalized at the C(2)-N position with extended carboxamide or amine linkers for the subsequent binding to technetium-99m and rhenium moieties, although the resulting complexes were shown neither to be transported through GLUT1 nor to satisfactorily inhibit hexokinase activity [169].

During the last decade, several carbohydrate-conjugated ligands suitable for chelation of technetium-99m and rhenium scaffolds (including not only tricarbonyl metal centers but also the simpler {M=O}\textsuperscript{3+} cores) have been designed. Nevertheless, actual targeting and exploitation of GLUTs to enhance cellular uptake of radioactive metal-glycoconjugates via the glycolytic pathway has not been reported so far. Efforts in the field have been anyway summarized in a recent comprehensive review [170].

### 5 Conclusions

The abnormal glucose metabolism of tumors can be successfully exploited for the targeted anticancer chemotherapy. In particular, “Trojan Horse”-type metallo-drugs functionalized with carbohydrates would combine the anticancer properties of metal-based therapeutics with the expected tumor selectivity provided by the coordinated glucose-like or glycomimetic substrate targeting GLUTs overexpressed in cancers. Such an approach has potential to induce the selective and improved intracellular transfer and delivery of the metal-containing cytotoxic agent only where needed.

As clearly shown above, within the field of carbohydrate-functionalized chemotherapeutics, a number of metal glycoconjugates have been reported to date but, apart from a very few exceptions, only routine cytotoxicity studies have been carried out, whereas the relationship between anticancer activity, cell uptake and capability to target GLUTs have been rarely evaluated.

Such surprising lack of detailed mechanistic studies has prompted us to summarize the most important results published so far in this review paper, which aims at inspiring other scientists in the field to drive this kind of research forward.

Remarkably, the actual breakthrough of the glyco-metal conjugation described here is not simply the use of metal compounds to treat cancer but the rational design of metal-based drugs that may be very effective, non-toxic and potentially selective towards cancer cells, their
enormous potential impact relying on the possible site-specific delivery in localized cancers, strongly improving effectiveness and minimizing side-effects.

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