Introduction

For decades, Pt(II) chemotherapeutics have been fundamental tools for the treatment of solid tumors.\textsuperscript{1-3} Although there have been extensive efforts to develop new Pt-based chemotherapeutics, there are currently only three approved by the FDA: cisplatin, carboplatin, and oxaliplatin.\textsuperscript{4-7} All FDA approved Pt chemotherapeutics are Pt(II) square planar complexes that cross-link DNA, ultimately leading to apoptosis in fast-dividing cells.\textsuperscript{1,8} This mechanism of action makes them highly effective at treating solid tumors. Even so, they have significant off-target toxicity that can result in a number of serious side effects including renal failure, hearing loss, and myelosuppression.\textsuperscript{1-5} Pt(II) chemotherapeutics are also susceptible to chemoresistance. This stems from multiple mechanisms, including decreased drug accumulation, cytotoxic sequestration, and resistance to DNA damage.\textsuperscript{6-12} Despite issues with toxicity and chemoresistance, Pt(II) complexes are used in nearly 50% of all chemotherapy regimens, making them some of the most widely used cancer drugs available.\textsuperscript{13}

A number of approaches have been attempted to mitigate off-target toxicity and chemoresistance of Pt(II) drugs. This includes using tumor-targeting groups, nanoconstructs, and selective release mechanisms.\textsuperscript{14-16} In recent years, Pt(IV) prodrugs have become a promising approach to alleviate off-target toxicity and reduce chemoresistance.\textsuperscript{17-19} Pt(IV) complexes are octahedral and inert compared to their Pt(II) square planar analogues. In an oxidizing extracellular environment Pt(IV) complexes remain inert. They can be reduced intracellularly to Pt(II), triggering the dissociation of a reactive Pt(II) drug from its axial ligands.\textsuperscript{15-19} A variety of groups can be incorporated as axial ligands to allow for tumor targeting, combination therapy, bioimaging, and controlled reduction of the Pt(IV).\textsuperscript{20-31} Sessler and coworkers were the first to demonstrate how Gd(III) complexes can be used synergistically with Pt(IV) prodrugs. Their Gd(III)-texaphyrin complexes have been used to increase tumor localization and mediate the reduction of Pt(IV) to Pt(II).\textsuperscript{20-21} However, we believe there is a significant opportunity to investigate Gd(III)-Pt(IV) mixed metal complexes for applications as theranostic agents.

Several examples of theranostic Pt(IV) prodrug complexes for dual chemotherapy and fluorescence imaging have been reported.\textsuperscript{24-27} Some of these probes can provide important information regarding drug delivery and subsequent reduction of the Pt(IV) complex in vitro. However, in vivo fluorescence imaging has limited clinical utility.\textsuperscript{32,33} The primary modality for imaging tumors is MRI, which allows for whole body, non-invasive imaging with excellent soft tissue contrast and spatial resolution.\textsuperscript{35-36} While a few examples of Gd(III)–Pt(IV) theranostics have appeared,\textsuperscript{37-39} to our knowledge there are no reported examples of Pt(IV) prodrugs containing a Gd(III) complex for contrast-enhanced MR imaging either in vitro or in vivo.

Here, we describe two Gd(III)–Pt(IV) theranostic agents that were synthesized by coupling a Gd(III) MR contrast agent axially to cisplatin and carboplatin-based Pt(IV) complexes. These agents are water soluble, cell permeable, and oxidatively stable, but are reduced under biologically relevant intracellular conditions to release the toxic Pt(II) payload and the Gd(III) MR agent (Scheme 1). These complexes are designed for
intracellular contrast enhancement of cancer cells, whereas typical Gd(III) contrast agents are limited to the extracellular space surrounding tumors. This Gd(III)–Pt(IV) platform possesses a second axial site that can be used to couple targeting groups for tumor specificity, drugs to combat chemoresistance, or fluorophores for multimodal imaging and validation.

Results and discussion
Synthesis and purification of the agents
Two Gd(III)–Pt(IV) agents, GP1 and GP2, were synthesized by coupling a Gd(III) complex, 1, with Pt(IV) complexes 2 and 3 respectively (Fig. 1A). Complexes 1, 2, and 3 were all synthesized following literature protocols. The structures of GP1 and GP2 are found in Fig. 1A. Both agents were purified by preparatory HPLC, characterized by HPLC-MS (see ESI†) and analyzed by ICP-MS to ensure the Gd : Pt ratio was 1 : 1.

Relaxivity measurements
The $T_1$ relaxivity ($r_1$) and $T_2$ relaxivity ($r_2$) of 1, GP1, and GP2 were measured at both low (1.41 T) and high (7 T) magnetic field strength in phosphate-buffered saline (PBS) to quantify how well they behave as MR contrast agents. Relativity values are summarized in Table 1. At 1.41 T, 1 had an $r_1$ of 4.1 mM$^{-1}$ s$^{-1}$ and an $r_2$ of 4.6 mM$^{-1}$ s$^{-1}$. At 7 T, the $r_1$ had a slight increase while the $r_2$ significantly increased, as expected at high field. The relaxivity values for 1 are well within the range of what is expected for a small molecule Gd(III) complex. At 1.41 T, GP1 and GP2 had an $r_1$ of 7.0 and 8.8 mM$^{-1}$ s$^{-1}$ and $r_2$ of 7.5 and 10.7 mM$^{-1}$ s$^{-1}$ respectively. At 7 T, there was little change in $r_1$ for both agents, while both $r_2$ values increased, as expected.

Compared to 1, both GP1 and GP2 had significantly increased relaxivity (both $r_1$ and $r_2$). This is possibly due to an increase in the rotational correlation time ($\tau_R$) or a change in the inner sphere hydration number ($\eta$) of Gd(III). The differences in relaxivity of GP1 and GP2 compared to 1 offers the possibility of monitoring reduction of the agents by MR at both high and low field strength. To test this, GP1, GP2, and 1 were incubated in 5 mM GSH in PBS and the relaxivity was measured (see ESI†). The relaxivity of each converged to the same value ($r_1$ of 4.4, 4.5, and 4.6 mM$^{-1}$ s$^{-1}$ for 1, GP1, and GP2 respectively), indicating the same Gd(III) species was formed after reduction. The significant change in $r_1$ upon reduction of GP1 and GP2 theoretically could be used to monitor intracellular reduction by MR. However, further testing needs to be done to determine if these agents are suitable for this application.

Stability and reduction of the Gd(III)–Pt(IV) complexes
Though most Pt(IV) complexes (see 2 and 3 in Fig. 1) are insoluble in most solvents, both GP1 and GP2 are readily soluble in aqueous solutions. To ensure both agents remain stable in aqueous media under various conditions, they were dissolved in PBS, two types of cell culture media (MEM and RPMI-1640), pH 5 H$_2$O$_2$, and porcine live esterase (PLE) in PBS and monitored over time by HPLC-MS.

Fig. 2A and B shows that over 48 hours, GP1 and GP2 both remained completely stable in PBS and pH 5 H$_2$O$_2$. This suggests that both agents can remain intact even in the most acidic conditions in cells, such as in lysosomes (pH 4.5–5). However, both agents also remained highly stable in MEM (≥92% intact) at 48 hours. GP1 and GP2 were mostly stable in the presence of PLE, and the slight decrease in stability that was observed (~10%) occurred on a much slower timescale than the reduction of both agents by GSH (Fig. 2C and D). It is unlikely that esterase cleavage is a competing intracellular dissociation mechanism.

In RPMI-1640, 33% of GP1 and 28% of GP2 were reduced to Pt(II) within 48 hours. Unlike MEM, which contains no glutathione (GSH), RPMI-1640 has 0.003 mM GSH. Though this is an extracellularly relevant concentration of GSH (0.002–0.02 mM), a minority of GP1 and GP2 are reduced...
over long periods of time. However, it is important to note that
at 6 hours, both agents are $96\%$ intact (i.e., they remain in the
Pt(IV) oxidation state). In vivo, an agent that does not get into cells
within this time frame will likely be renally cleared before it is
reduced. Therefore, within the time frame relevant for in vivo
experiments, GP1 and GP2 stay intact and stable in extracellu-
larly relevant conditions.

Under reducing conditions both agents rapidly converted
to a monomeric Gd(III) complex and a Pt(II) drug. Each agent
was incubated with 5 mM GSH and 5 mM ascorbate at 37 °C
to mimic intracellular conditions. Fig. 2C and D shows that
both agents are rapidly reduced by GSH at these concentra-
tions ($\approx 94\%$ reduction in less than an hour). As expected,
GP1 and GP2 are also reduced by ascorbate, albeit it at
a much slower rate. This is not surprising, as ascorbate is
a weaker reducing agent. It is clear from these results that
under conditions similar to those inside cells, both agents
are reduced, releasing a Gd(III) contrast agent and Pt(II)
chemotherapeutic.

Cytotoxicity of the agents
To assess the cytotoxicity of GP1 and GP2 in vitro, cell viability
assays were performed to determine the IC$_{50}$ concentrations in
two cancer cell lines (A2780, HeLa, and MCF-7). Table 2
summarizes the IC$_{50}$ concentrations of both agents compared
to those of cisplatin and carboplatin. Cells were incubated with
cisplatin and GP1 for 48 h and carboplatin and GP2 for 72 h to
compensate for the inherent decreased potency of carboplatin
compared to cisplatin. GP1 had an IC$_{50}$ of 29.8 $\mu$M in A2780
cells, 49.3 $\mu$M in HeLa cells, and 113 $\mu$M in MCF-7 cells. For all
cell lines, GP1 was less toxic than cisplatin but followed the
same trend of highest toxicity in A2780 cells and least toxic in
MCF-7 cells. GP1 releases cisplatin intracellularly, therefore the
apparent difference in toxicity of the two is likely due to
decreased cell permeability of GP1 caused by the Gd(III)
complex. However, because GP1 is inert in the extracellular
matrix, higher doses can be safely administered to account for
the decreased cell permeability.

GP2 had an IC$_{50}$ of 55.0 $\mu$M in A2780 cells, 258 $\mu$M in HeLa
cells, and 382 $\mu$M in MCF-7 cells. The decreased toxicity of GP2
compared to GP1 is expected because carboplatin is known to
be significantly less reactive than cisplatin. GP2 was similarly
less toxic than carboplatin, but followed the same trend of
highest toxicity in A2780 cells and lowest toxicity in MCF-7 cells.
The decreased toxicity compared to carboplatin is again
attributed to decreased cell permeability due to the presence of
the Gd(III) complex.

These results demonstrate that GP1 and GP2 are cytotoxic in
two different cancer cell lines. Both agents show similar
trends in toxicity as their Pt(II) analogues, which suggests that
upon entering the cells they are reduced and behave like typical Pt(II) chemotherapeutics.

Accumulation of the Gd(III)–Pt(IV) agents in cells

Accumulation of GP1 and GP2 in cells was measured by concentration-dependent uptake experiments in A2780 and HeLa cells. Individual concentration-dependent uptake graphs are found in the ESI.† Table 3 compares the accumulation of Gd and Pt in A2780 and HeLa cells that were incubated with GP1, GP2, cisplatin, and carboplatin near their IC50 concentrations. For comparison, both cell lines were dosed with complex 1 at similar concentrations as GP1 and GP2. The results of these uptake experiments demonstrate several important points. First, the accumulation of Gd in both cell lines for both agents is higher than what is typically considered the amount necessary for detection by MR (high μM concentrations).22,33 This suggests that GP1 and GP2 can significantly enhance intracellular MR contrast. Typical Gd(III) complexes alone are not cell permeable, therefore the Pt(IV) complexes likely make it possible for GP1 and GP2 to get into cells. This is evidenced by the significant increase in cellular uptake of GP1 and GP2 compared to complex 1 in both cell lines.

Second, intracellular Pt levels at the IC50 concentrations were similar between GP1 and cisplatin and GP2 and carboplatin. From a therapeutic standpoint, the agents behave like cisplatin and carboplatin once they enter cells and are reduced from Pt(IV) to Pt(II). These results support that the higher IC50 concentrations of GP1 and GP2 compared to

### Table 2
IC50 concentrations of cisplatin, carboplatin, GP1, and GP2 in various cell lines

| Complex   | IC50 (μM) | A2780 | HeLa | MCF-7 |
|-----------|-----------|-------|------|-------|
| Cisplatin | 7.6 ± 2.3 | 14.7 ± 1.2 | 22.4 ± 2.0 |
| Carboplatin | 15.3 ± 5.8 | 71.2 ± 4.9 | 124 ± 4 |
| GP1       | 29.8 ± 2.5 | 49.3 ± 1.3 | 113 ± 4 |
| GP2       | 55.0 ± 2.9 | 258 ± 5.0 | 382 ± 6 |

### Table 3
Accumulation of Gd and Pt in A2780 and HeLa cells when incubated with GP1, GP2, cisplatin, and carboplatin near their IC50 concentrations and 1 at 100 μM for 24 h

| Complex | A2780 cells | HeLa cells |
|---------|-------------|------------|
| Gd      | Pt          | Gd         | Pt         |
| GP1     | 2.5 ± 0.3   | 0.20 ± 0.03| 5.7 ± 1.9  | 0.17 ± 0.01 |
| GP2     | 1.4 ± 0.2   | 0.38 ± 0.1 | 1.1 ± 0.2  | 0.30 ± 0.06 |
| 1       | 0.26 ± 0.02 | N/A        | 0.21 ± 0.01| N/A         |
| Cisplatin | N/A        | 0.21 ± 0.02| N/A        | 0.27 ± 0.02 |
| Carboplatin | N/A        | 0.22 ± 0.02| N/A        | 0.60 ± 0.11 |
cisplatin and carboplatin are caused by decreased cell-permeability, not a decrease in intracellular toxicity. It is clear that both GP1 and GP2 penetrate cells well enough to provide sufficient MR-Gd(III) concentrations for imaging and therapeutically relevant Pt concentrations in cells at low incubation concentrations.

Finally, there is a significant preferential accumulation of Gd compared to Pt from both agents in both cell lines. The difference in accumulation of the two is possible because they dissociate from one another after the intracellular reduction of Pt(IV) to Pt(II). For GP1, a 13-fold higher accumulation of Gd than Pt in A2780 cells and 34-fold higher Gd(III) accumulation in HeLa cells was observed. For GP2, Gd accumulation was 3.7-fold higher in both A2780 and HeLa cells. These results suggest that Gd is effluxed to a lesser extent than Pt. When GP1 and GP2 are reduced intracellularly, the cell impermeable charged Gd(III) complex is likely prevented from exiting the cells as readily as the cell permeable Pt(II) complexes. This is of particular consequence for the ability of GP1 and GP2 to act as MR contrast agents because higher cellular amounts of Gd(III) increase MR contrast.

Cell uptake of GP1 and GP2 was additionally measured in a time-dependent manner in A2780 cells. Fig. 3 demonstrates that the accumulation of both Gd and Pt from both agents is directly proportional to time. In these experiments, higher accumulation of Gd compared to Pt from both agents is consistent with a higher rate of efflux of Pt. These results also suggest MR-relevant amounts of Gd from both agents accumulate in cells within a few hours. This is promising for the prospect of imaging within the time frame relevant for in vivo experiments.

**MR imaging of A2780 and HeLa cell pellets**
To quantify the ability of GP1 and GP2 to enhance MR contrast intracellularly, MR cell pellet imaging experiments were performed. A2780 and HeLa cells were incubated with IC50 concentrations of GP1 and GP2 for 6 hours then imaged in a 7 T MR scanner. The relaxation rate (R1), which is defined as 1/T1, and is directly proportional to MR contrast, of each cell pellet was determined and compared to control cells that were untreated, incubated with 100 µM complex 1, or incubated with IC50 concentrations of cisplatin.

Fig. 4 demonstrates that GP1 and GP2 significantly enhance the intracellular MR contrast of both A2780 and HeLa cells when dosed at concentrations near the IC50. GP1 increased the R1 by 36% in A2780 cells and 48% in HeLa cells compared to the untreated controls. GP2 increased the R1 by 26% in A2780 cells and 23% in HeLa cells. Treating cells with similar concentrations of complex 1 and IC50 concentrations of cisplatin resulted in minimal increases in R1. This supports that the observed contrast enhancement by GP1 and GP2 is a result of the agents effectively accumulating in cells, something 1 cannot do alone. Furthermore, any physiological changes in the cells caused by the presence of a Pt(II) drug have little effect on the MR contrast. Therefore, the contrast enhancement is a result of intracellular Gd(III).

![Fig. 3](image-url) (A) Accumulation of Gd and Pt in A2780 cells incubated with 65 µM GP1 over time. (B) Accumulation of Gd and Pt in A2780 cells incubated with 62.5 µM GP2 over time. In both cases, accumulation of Gd was significantly higher than Pt.

![Fig. 4](image-url) (A) MR imaging of A2780 cell pellets at 7 T. IC50 concentrations of GP1 and GP2 significantly enhanced the intracellular contrast of A2780 cells (increase in R1) compared to the untreated control cells while 1 and cisplatin had a minimal effect. (B) MR imaging of HeLa cell pellets at 7 T. IC50 concentrations of GP1 and GP2 significantly enhanced the intracellular contrast of HeLa cells compared to the untreated control cells while 1 and cisplatin had a minimal effect.
Notably, the cell pellet experiments were performed within a time frame relevant for in vivo MR imaging (6 hours). These results are very promising for the prospect of using Gd(III)–Pt(IV) theranostics like GP1 and GP2 for in vivo MR imaging.

Conclusions

We have described the synthesis, characterization and cellular uptake of two new Gd(III)–Pt(IV) agents. GP1 and GP2 represent the first examples of Gd(III)–Pt(IV) agents that are simultaneously MR contrast agents and are reduced to provide chemotherapy. Of the two agents, GP1 is most promising as it exhibits greater cellular toxicity, higher intracellular accumulation of Gd(III) and better MR contrast enhancement in vitro. Future work will focus on demonstrating the in vivo efficacy of these agents for both imaging and treatment.

Conflicts of interest

There are no conflicts of interest to declare.

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