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# Lessons from metals-containing drugs in diagnostic, and theranostic applications for future development of metal-containing non-conventional therapeutics: vanadium compounds for intratumor administration

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The development of novel diagnostic, theranostic, and therapeutic agents drastically improved human health, human lifespan, and quality of life. In 2024, 15 of the 50 (30%) new drugs approved by the Food and Drug Administration (FDA) were developed for the treatment of cancer. Despite encouraging examples of platinum-based anticancer drugs and many metal-based diagnostic agents for cancer, only a few metal-based drugs have translated to clinical success. Therapeutic drugs share many properties with diagnostic and theranostic agents, such as distribution and uptake, but differ in one key aspect: stability. Stability is key to the action of the potential drug and impact excretion and metabolism, and these properties illustrate the differences between diagnostic and therapeutic agents. That is, diagnostics are inherently stable and not metabolized whereas therapeutics are commonly administered as pro-drugs where metabolism is a common and often important aspect of their mode of action. In this perspective, we point to a novel administration strategy, such as intra-tumoral injections, for which highly reactive compounds, such as metal-based compounds would be desirable as long as the decomposition products are non-toxic. Investigations into a class of vanadium compounds for administration in difficult-to-treat cancers, such as glioblastomas, are briefly described here.

## KEYWORDS

therapeutics, diagnostics, theranostic agents, metal coordination complexes, stability, toxicity, MRI contrast agents, radiopharmaceuticals

## Introduction

Modern medicine has been increasingly successful in treating diseases and genetic disorders, producing a range of pharmaceuticals for various conditions. As a result, pre-clinical studies demonstrating efficacy is no longer sufficient to reflect the clinical success of a drug (Seyhan, 2019). Modern drug development must consider toxicity and side effects, formulation, accessibility and increasingly demanding regulations for a drug to translate to widespread clinical adoption. In this perspective, we aim to highlight the current landscape and recent advances in state-of-the-art cancer drug development (Ronconi and Sadler,

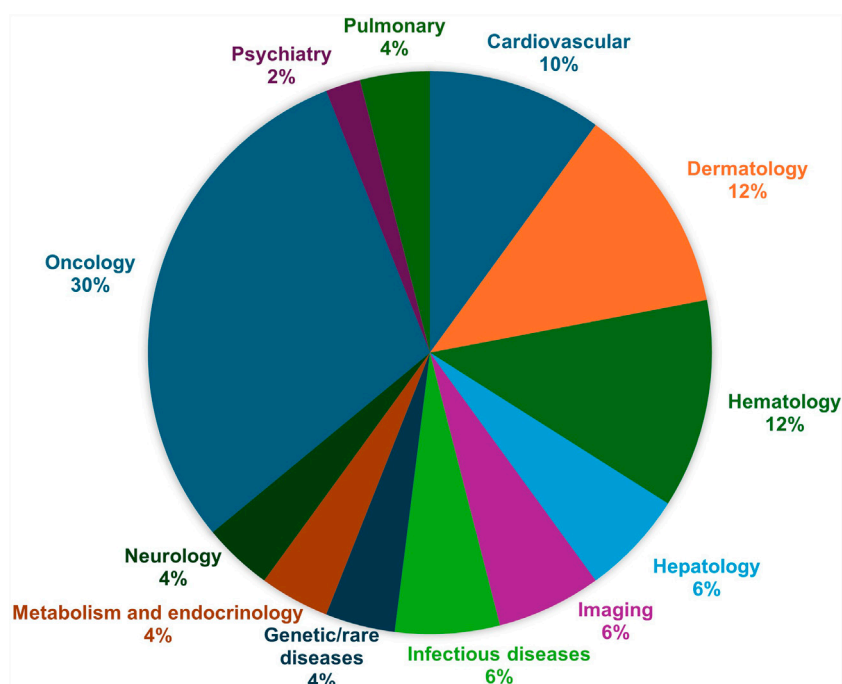


FIGURE 1  
The United States of America FDA approvals by therapeutic areas in 2024 (Mullard, 2025).

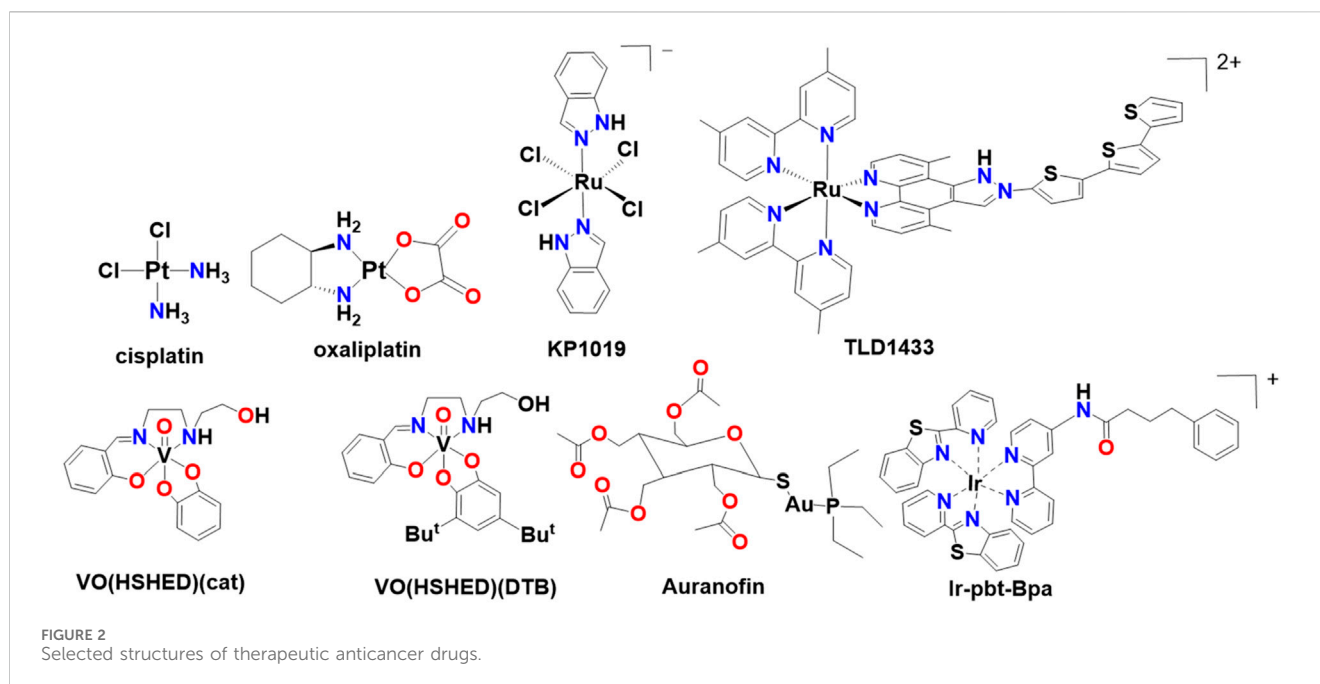
2007; Jomova et al., 2024; Sen et al., 2022; Li et al., 2025; Nidhi et al., 2025; Zahirović et al., 2024; Abdullah et al., 2024; De Sousa et al., 2023; Wang et al., 2023; Skos et al., 2024; Scattolin et al., 2025; Crans and Kostenkova, 2020; Crans, 2015; Zhang and Sadler, 2017; Gunaydin et al., 2021; Anthony et al., 2020) and diagnostic agents (Wu et al., 2025; Kim and Nimse, 2025; Rex et al., 2025; Stasiuk and Long, 2013; Boswell et al., 2004; Janib et al., 2010; Terreno et al., 2010; Kostelnik and Orvig, 2019; Wahsner et al., 2019; Caravan et al., 1999; Hancu et al., 2010) with a focus on metal complexes used as MRI contrast agents (Janib et al., 2010; Terreno et al., 2010; Wahsner et al., 2019; Caravan et al., 1999; Hancu et al., 2010; Na et al., 2009; Jeon et al., 2021; Runge, 2017; Fraum et al., 2017; Ramalho et al., 2016; Chen et al., 2022; Müssig et al., 2021) and radiopharmaceuticals (Stasiuk and Long, 2013; Boswell et al., 2004; Kostelnik and Orvig, 2019; Rathmann et al., 2019; Yang et al., 2024; Zhang et al., 2025; Holland et al., 2009; Duatti, 2021; Crişan et al., 2022; Kelkar and Reineke, 2011; Gutfilen et al., 2018; Hennrich and Benešová, 2020; Zboralski et al., 2022; Kraus et al., 2022; Krasnovskaya et al., 2023; Kelly et al., 2020). Additionally, we will describe the properties of a few metal-based therapeutics and compare them to a new class of vanadium-based Schiff base catecholate complexes that we have been investigating for potential use for intratumoral administration (Levina et al., 2020; Levina et al., 2022; Bates et al., 2025). Finally, we will compare therapeutic and diagnostic drugs with the aim of gaining a deeper understanding of the desirable properties of successful and potential drugs.

In 2024, 50 new small molecule, biologic, and oligonucleotide therapeutics were approved by the Center for Drug Evaluation and Research in the United States (FDA) (Mullard, 2025). Figure 1 shows

the distribution of novel drug approvals in the United States in 2024, indicating cancer therapeutics comprise 30% of newly introduced drugs. Many of the therapeutic areas show a higher number of new drugs in 2024 than the 5-year average (Mullard, 2025). Beyond small molecules, the FDA's Center for Biologics Evaluation and Research (CBER) added an additional set of cell and gene therapies, vaccines, and blood products which received approvals. These substances provide an alternative approach to cancer treatment which are well tolerated by the immune system and this class of drugs are called T-cell receptor therapy and Afamitresgene autoleucel is an example of a cancer related drug approved in spring of 2025 (Mullard, 2025).

Traditionally, small molecule drugs are subject to Lipinski's rule of five which were developed using computational analysis of successful small molecule drugs and drug candidates (Lipinski, 2016). These guidelines include the following criteria: a molecular weight that is less than 500 Da, a maximum level of hydrophobicity determined by the octanol-water partition coefficient (logP) less than 5; and the molecule must contain no more than 5 hydrogen bond donors, and no more than 10 hydrogen bond acceptors. Other approaches to characterizing drug properties have been reported focusing on structural features and frequency of false positive and negative hits in drug screens (Nelson et al., 2017; Sun et al., 2021). Metal-based therapeutics rarely adhere to Lipinski's rules because the metal-based drugs are generally less stable *in vivo* than organic drugs, releasing metal ions, which can potentially create reactive oxygen species when participating in redox chemistry (Dinda et al., 2025; Aurelia et al., 2023).

Many diagnostic agents have a metal ion as part of their chromophore enabling their detection via UV-visible, fluorescence, phosphorescence, or other types of spectroscopic



methods. *In vivo* metal-based diagnostic agents fall into three categories: X-ray contrast agents (Yu and Watson, 1999; Lusic and Grinstaff, 2013), MRI contrast agents (Terreno et al., 2010; Wahsner et al., 2019; Caravan et al., 1999; Hancu et al., 2010; Na et al., 2009; Jeon et al., 2021), and radiotracers (Kostelnik and Orvig, 2019; Rathmann et al., 2019; Yang et al., 2024; Zhang et al., 2025; Holland et al., 2009; Duatti, 2021; Crişan et al., 2022). In 1988, the first metal-based magnetic resonance imaging (MRI) contrast agent was approved by the FDA for clinical use, gadolinium-based contrast agent (GBCA) gadopentetate dimeglumine (Gd-DTPA, Magnevist, Figure 2) (Caravan et al., 1999). Metal-based diagnostic agents must be very stable under physiological conditions to prevent metal leaching and potential cytotoxicity. Furthermore, a new field has emerged combining a diagnostic (“nostic”) and therapeutic (“thera”) called theranostics where the agents both diagnose and treat at the same time (Janib et al., 2010; Kostelnik and Orvig, 2019; Zhang et al., 2025; Crişan et al., 2022; Kelkar and Reineke, 2011; Gutfilen et al., 2018).

## Therapeutic drug processing and drug formulation

The pharmacological properties of a drug include its pharmacodynamic and pharmacokinetic properties. The pharmacodynamic properties of a drug involve “what a drug does” to a biological system. The potency of a drug is the amount (dose) of drug required to produce the intended effect (intensity/maximum). The efficacy of a drug is its capacity (intensity/maximum) to produce the effect. It is important to recognize that the success of a drug requires much more than high potency (low dose) and favorable efficacy. The pharmacokinetic properties of a drug are the processes which take place upon drug administration. Pharmacokinetics is defined by four critical processes: administration, distribution, metabolism,

and excretion, which is abbreviated ADME. Each of these processes is important to the success of a drug and can be impacted by the method of administration and its formulation (delivery vehicle).

There are many different administration methods, and the specific properties of a particular drug must be considered when choosing the administration method and delivery vehicle (Wen et al., 2015). For example, if the drug is administered orally, it must be able to survive the acidic environment in the stomach. Many anticancer drugs are administered intravenously so they must be able to survive circulation and metabolism that can take place in blood. Drug delivery approaches do not change the fundamental pharmacodynamic properties of a drug, but they can modify its pharmacokinetic properties, which can impact its pharmacodynamic performance (Wen et al., 2015; Duan et al., 2016). For example, the initial formulation of chemotherapy drug Vincristine resulted in rapid clearance and was ultimately not approved by the FDA. However, when encapsulated in sphingomyelin/cholesterol liposomes, Vincristine’s clearance rate decreased and resulted in increased efficacy against tumor cells. The modified formulation was approved by the FDA in 2012 (Silverman and Deitcher, 2013), and Vincristine is still administered with high survival rates particularly in protocols with other drugs when treating various leukemias. At this point, few metal-based pharmaceuticals make it to the clinic. However, as novel treatment strategies become more common, the potential benefits of metal-based pharmaceuticals can outweigh the risks, as exemplified by the dramatic increase in number of clinical trials involving intratumoral administration and metal-based drugs (Levina et al., 2022; Bates et al., 2025).

## Metal-based therapeutic drugs

*Cis*-diamminedichlorido-platinum (II) (cisplatin, Figure 2) has been used in the clinic for >40 years, far beyond the 20-year original

patent lifetime. Platinum (Pt)-based drugs are among the most frequently used cancer therapeutic agents (Rottenberg et al., 2020). Pt-based drugs form adducts with DNA, preventing DNA repair enzymes from removing Pt and preventing mitosis (Kartalou and Essigmann, 2001). Cisplatin can form monoadducts, intrastrand, or interstrand cross-links with both single and double-stranded DNA, although research has demonstrated that Pt-compounds engage in multiple other mechanisms of action which result in their antiproliferative properties (Liu et al., 2024; Manioudakis et al., 2019). The 1,2-intrastrand crosslinks with DNA double helices are particularly devastating for cells (Kartalou and Essigmann, 2001), but other mechanisms also cause multiple side effects such as vomiting, nephrotoxicity, and neurotoxicity in patients (Liu et al., 2024; Manioudakis et al., 2019). However, newer Pt-drugs, such as cis-[(1R,2R)-1,2-cyclohexanediamine-N,N']-[oxalato (2-)-O,O'] platinum (oxaliplatin, Figure 2), have been developed with increased solubility, improved efficacy, and decreased toxicity compared to cisplatin and both drugs are still used in the clinic. Co-administering cisplatin with lipids reduces its toxicity, and many novel formulations of Pt-drugs are currently being investigated in clinical trials (Duan et al., 2016; Doucette et al., 2016).

Many metal compounds are effective antiproliferative agents and excellent reviews have been written on this topic including coordination complexes with ruthenium, gold, copper, iridium and osmium (Wang et al., 2023; Skos et al., 2024; Scattolin et al., 2025; Anthony et al., 2020; Kozieł et al., 2024), a few representative compounds are shown in Figure 2. Metal ions such as rhodium, rhenium, cobalt, manganese, and vanadium have also been explored and selected vanadium complexes are also shown in Figure 2. We refer the readers to reviews for additional details on these classes of drugs (Ronconi and Sadler, 2007; Jomova et al., 2024; Sen et al., 2022; Li et al., 2025; Nidhi et al., 2025; Zahirović et al., 2024; Abdullah et al., 2024; De Sousa et al., 2023; Crans and Kostenkova, 2020; Crans, 2015; Zhang and Sadler, 2017; Anthony et al., 2020; Rottenberg et al., 2020; Thota et al., 2018). Suffice to say that two Ru-compounds (KP1019 and TLD1433), shown in Figure 2, are currently in clinical trials (Thota et al., 2018). Both these drugs have activity against Pt-resistant cells and act through a different mechanism than Pt-drugs. In addition, Au-complexes such as Auranofin (Celegato et al., 2015), and other metal-based complexes including Ir-ptb-Bpa (Wang et al., 2023) are being investigated in pre-clinical studies (Figure 2). The success of these compounds supports the current and continued future interest in metal-based anticancer drugs. In the following sections we will describe diagnostic and theranostic agents and conclude this perspective with potential therapeutic vanadium anticancer agents designed for intratumoral injections.

## Metal-based diagnostics

Metal complexes have been important tools in the diagnosis of disease for over a century. Metal-based diagnostics share many similarities with therapeutics in that they are designed for imaging a particular target tissue, have sufficient biological half-life, be minimally disruptive to biological processes, show low toxicity, and be excreted or metabolized after imaging is complete.

However, there is one major difference from the therapeutics, particularly with metal-based MRI contrast agents and radiopharmaceuticals, they are typically designed to NOT be metabolized. The structures for selected MRI contrast agents and radiopharmaceuticals are shown in Figure 3.

## Magnetic Resonance Imaging (MRI) Contrast Agents

Today, about 40% of all MRI scans utilize Gadolinium-based Contrast Agents (GBCA) and they remain one of the most successful examples of inorganic drugs, particularly for detecting cancer (Wahsner et al., 2019). While other lanthanides have larger magnetic moments,  $Gd^{3+}$  has the maximum number of unpaired electrons ( $f^7$ ) of any stable ion, making it ideal for use as a paramagnetic MRI contrast agent. Coordinated water ligands must be able to rapidly exchange with the cellular environment to shorten  $T_1$  relaxation time, providing contrast. As such, there has been some effort made to increase the number of water ligands coordinated to Gd (increasing contrast), but there is significant cost associated with the stability of the complex (Wahsner et al., 2019), another important factor for the success of a GBCA MRI contrast agent.

GBCAs typically belong to two general classes depending on whether they contain linear or macrocyclic ligands. Macrocyclic ligands form significantly more stable metal complexes than the linear complexes as evidenced from the leakage that the latter complexes exhibited in retrospective studies (Grobner, 2006). Additional studies have reported that linear and neutral complexes are less stable under physiological conditions compared to macrocyclic and ionic complexes (Runge, 2017; Fraum et al., 2017). These studies showed that repeated administration of linear GBCAs such as Gd-DTPA led to Gd(III) deposition in the central nervous system (CNS). Gd(III) deposition is associated with nephrogenic systemic fibrosis (NSF), particularly in patients with renal impairment (Ramalho et al., 2016). This discovery has led to macrocyclic GBCAs largely supplanting their linear counterparts in the clinic.

Superparamagnetic Iron Oxide Nanoparticles (SPIONs) and their manganese-based counterparts are composed of a metal oxide core surrounded by a biocompatible surface polymer. While superparamagnetism can lead to a decrease in both  $T_1$  and  $T_2$  relaxation times, SPIONs have primarily been used as  $T_2$  contrast agents (Chen et al., 2022). In SPIONs, smaller core size increases specific surface area, allowing for increased interactions with water protons, increasing longitudinal relaxivity ( $r_1$ ) while decreasing magnetization and transverse relaxivity ( $r_2$ ). Larger  $r_1$  values and a smaller  $r_2/r_1$  ratio results in a better  $T_1$  contrast agent (Chen et al., 2022). Careful balancing of core size, polymer coating, hydrodynamic diameter, and several other factors (Jeon et al., 2021) could produce an ultrasmall SPION (<5 nm) that could compete commercially with GBCAs used for  $T_1$  contrast or even produce a switchable  $T_1/T_2$  contrast agent through reversible agglomeration (Chen et al., 2022; Müssig et al., 2021). While SPIONs have primarily been investigated as diagnostics and iron replacement therapeutics, there is significant interest in their development as theranostic agents for cancer therapy, exploiting a variety of cell death mechanisms (Vangijzegem et al., 2023).



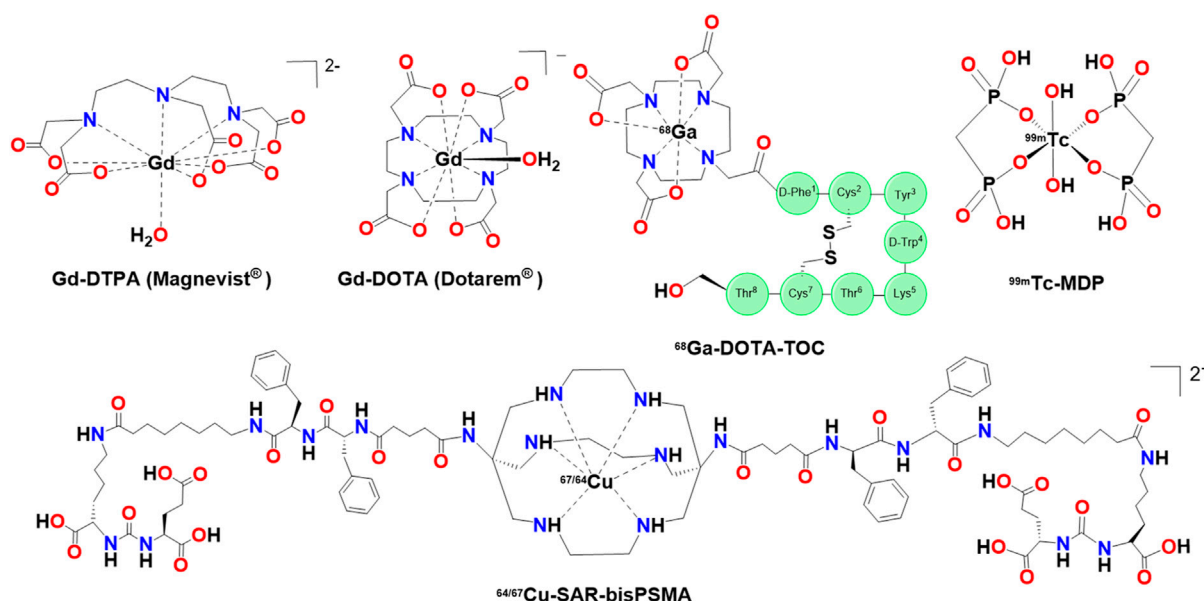


FIGURE 3  
Selected structures of Gadolinium-based MRI contrast agents, a technetium (Tc) radiopharmaceutical and a Cu-radiotheranostic agent.

## Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) Diagnostics

The general radiotracer  $^{18}\text{F}$ FDG (fluorodeoxyglucose) is the most prevalent agent used in PET due to increased glucose metabolism in the tumor microenvironment. More specialized, targeted  $^{68}\text{Ga}$  tracers are the leading application of radiometals in PET (Kostelnik and Orvig, 2019). SPECT requires a  $\gamma$ -emitting radionuclide while PET requires a  $\beta^+$ -emitting (positron) radionuclide. It is generally accepted PET provides better spatial resolution and sensitivity than SPECT, but utilization of  $^{99\text{m}}\text{Tc}$  in SPECT still surpasses all PET radiotracers for the detection of cancer (Duatti, 2021). This can primarily be attributed to comparatively low costs associated with SPECT, an abundance of FDA-approved radiopharmaceuticals targeting a large variety of biological systems, and the accessibility of  $^{99\text{m}}\text{Tc}$  radionuclide production due to convenient  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generators (Rathmann et al., 2019). Choice of radionuclide is extremely important for the success of a radiopharmaceutical. Without accessible and affordable cyclotron targets or generators for a radionuclide, a radiopharmaceutical does not have a chance at widespread clinical adoption.

$^{99\text{m}}\text{Tc}$  is a nearly perfect radionuclide for nuclear medicine. It is a  $\gamma$ -emitter with a moderate half-life ( $t_{1/2} = 6\text{ h}$ ) with the potential to be produced off-site. Many  $^{99\text{m}}\text{Tc}$  radiopharmaceuticals are available in convenient freeze-dried formulation kits which reduce the production burden for administration of Technetium-based radiopharmaceuticals. Success of  $^{68}\text{Ga}$ -based radiopharmaceuticals in the diagnosis of neuroendocrine tumors (NETs) and prostate tumors has renewed interest in the use of  $^{99\text{m}}\text{Tc}$  for similar applications (Duatti, 2021; Crişan et al., 2022). When factoring in recent advancements in SPECT technology (Duatti, 2021),  $^{99\text{m}}\text{Tc}$  still has a key role to play in nuclear medicine.

$^{68}\text{Ga}$  is a  $\beta^+$ -emitter with a relatively short half-life ( $t_{1/2} = 68\text{ min}$ ). The widespread use of  $^{68}\text{Ga}$  is largely attributed to accessibility of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators and the success of the first  $^{68}\text{Ga}$  radiotracers  $^{68}\text{Ga}$ -DOTA-TATE and  $^{68}\text{Ga}$ -DOTA-TOC (Figure 3) (Hennrich and Benešová, 2020). Like GBCAs, most radiometals necessitate the use of chelators, particularly macrocyclic chelators like DOTA, to maintain required biological stability.  $^{68}\text{Ga}$ -DOTA-TATE and  $^{68}\text{Ga}$ -DOTA-TOC are peptide-based somatostatin analogs and bind to somatostatin receptors which are highly expressed in NETs. Prostate-specific membrane antigen (PSMA) is expressed on the surface of prostate tumors and  $^{68}\text{Ga}$ -PSMA-11 is one of the most successful PSMA imaging agents (Kostelnik and Orvig, 2019). The small molecule drug  $^{68}\text{Ga}$ -FAPI (and its derivatives) and the macrocyclic analogue,  $^{68}\text{Ga}$ -FAP-2286 are peptide-based radiotracers targeting fibroblast activation protein- $\alpha$  (FAP), which is upregulated in the tumor microenvironment. FAPI and FAP-2286 are promising radioligands due to selective expression of FAP in healthy cells. Additionally, FAPI and FAP-2286 radiotracers outperformed  $^{18}\text{F}$ FDG in some pre-clinical studies (Zboralski et al., 2022).  $^{68}\text{Ga}$ -DOTA-CPCR4-2 (Pentixafor) is a peptide-based radiotracer targeting C-X-C chemokine receptor 4 (CXCR4) which is overexpressed in more than 30 different types of cancer and can be particularly effective for diagnosing various types of blood cancer (Kraus et al., 2022). Though these (FAPI, FAP-2286, and Pentixafor) radiopharmaceuticals are not approved by the FDA, they remain promising and active research areas (Zhang et al., 2025).

$^{64}\text{Cu}$ -DOTA-TATE is one of only two copper radiotracers currently approved by the FDA. Studies have shown that  $^{64}\text{Cu}$ -DOTA-TATE enables detection of more cancerous lesions (Krasnovskaya et al., 2023) than  $^{68}\text{Ga}$ -DOTA-TOC and  $^{64}\text{Cu}$  has a significantly longer half-life ( $t_{1/2} = 12.7\text{ h}$ ) compared to  $^{68}\text{Ga}$ .  $^{64}\text{Cu}$  radiotracers can be better options for hospitals that do not have cyclotron production facilities and/or transport of radionuclides is

necessary (Holland et al., 2009), particularly if a hospital is not located in a major city with third party radionuclide production facilities. Additionally,  $^{64}\text{Cu}$  as a radionuclide is appealing for radioimmunodiagnostic applications because the pharmacokinetics tend to be slower (Yang et al., 2024).

$^{89}\text{Zr}$  is a kinetically inert isotope with a long half-life ( $t_{1/2} = 78.4$  h) and has primarily been used as a radiotracer upon conjugation with monoclonal antibodies (mAbs). Trastuzumab was the first FDA-approved companion drug mAb to utilize  $^{89}\text{Zr}$ .  $^{89}\text{Zr}$ -trastuzumab targets human epidermal growth factor receptor 2 (HER2) which is upregulated in some tumors, particularly breast cancer (Zhang et al., 2025).  $^{89}\text{Zr}$ -based mAb radiotracers have also been used to target cluster of differentiation proteins 3, 4, 8, 20, and 30 to diagnose a wide variety of cancers (Zhang et al., 2025). Differentiation proteins are specific for different types of cells, allowing for the design of versatile mAb radiopharmaceuticals. Application of mAb PET radiopharmaceuticals is one of the fastest growing areas in both radiodiagnosics and radiotherapeutics.

## Radiotheranostics

Radiotheranostics is a field in which a radiodiagnostic is combined with a radiotherapeutic. While  $^{90}\text{Y}$  has been used extensively in radioconjugates with mAbs,  $^{177}\text{Lu}$  to-date is the overwhelmingly preferred radiometal for targeted radiotherapy, particularly in terms of pre-clinical studies.  $^{177}\text{Lu}$  is a  $\beta^-$ -emitter with a long half-life ( $t_{1/2} = 6.7$  days).  $^{177}\text{Lu}$ -DOTA-TATE has been approved by the FDA for use in conjunction with radiotracers such as  $^{68}\text{Ga}$ -DOTA-TOC, DOTA-TATE, and  $^{64}\text{Cu}$ -DOTA-TATE for the treatment of neuroendocrine tumors.  $^{177}\text{Lu}$ -PSMA-617 was approved by the FDA for use in conjunction with radiotracers such as  $^{68}\text{Ga}$ -PSMA for the treatment of prostate cancer. Since these approvals,  $^{177}\text{Lu}$ -based therapeutics have exploded in popularity and therapeutic complements can be found for many of the  $^{68}\text{Ga}$ -based (and  $^{18}\text{F}$ ) radiotracers currently in development.

Two isotopes of copper,  $^{64}\text{Cu}$  and  $^{67}\text{Cu}$ , have generated some interest as radiotheranostic agents. While  $^{64}\text{Cu}$  has primarily been used in PET as a radiotracer, it also emits  $\beta^-$  radiation, enabling theranostic applications (Gutflen et al., 2018). On 19 February 2025 the FDA approved with a fast-track designation a new radiotheranostic combo  $^{64/67}\text{Cu}$ -SAR-bisPSMA for the diagnosis and treatment of prostate cancer. The diagnostic and antineoplastic activity of  $^{64/67}\text{Cu}$ -SAR-bisPSMA is achieved through a sarcophagine (SAR)-based chelator bound to either  $^{64}\text{Cu}$  for the diagnostic or the  $\beta^-$ -emitting radioisotope  $^{67}\text{Cu}$  which is linked to two PSMA-binding motifs.  $\text{Cu(II)}$  complexes can be unstable *in vivo* with some chelators, such as DOTA, but forms more stable complexes with SAR (Kelly et al., 2020). Additionally,  $^{64/67}\text{Cu}$ -SAR-bisPSMA contains two PSMA-motifs which increases affinity for the receptor. Even though the combination of  $^{64/67}\text{Cu}$  provides many opportunities for the development of versatile radiotheranostic agents due to a single ligand framework for both radionuclides, this is only the third copper radiopharmaceutical approved by the FDA.

## Vanadium compounds for use in intratumoral administration

Intratumoral administration is an example of a currently less commonly used method for therapeutic administration. This method avoids circulation of the drug in the blood and any metabolism or degradation that could take place before the drug reaches its target. We have recently been investigating vanadium(V) Schiff base catecholate complexes and their antiproliferative properties to be used for intratumoral administration in difficult-to-treat cancers such as brain cancers (specifically glioblastoma (Levina et al., 2020)) and several other cancers (Levina et al., 2022; Crans et al., 2019). There are multiple classes of vanadium compounds that have been reported to have antiproliferative effects in various types of cancerous cells. Specifically, we are referring to reports describing a range of different classes of vanadium compounds with anticancer activities including dipicolinate oxovanadium(IV) (Choroba et al., 2023), 3-hydroxy-4(1H)-pyridinone oxovanadium(IV) complexes (Kostenkova et al., 2023), vanadium(III)-L-cysteine (Basu et al., 2017), vanadocene dichloride (Rozzo et al., 2017), acetylacetonateoxydiacetato-oxidovanadium(IV) Complexes coordinated to N-containing aromatic compounds (Chmur et al., 2025), non-oxido vanadium(IV) complexes featuring tridentate ONS chelating S-alkyl/aryl-substituted dithiocarbamate ligands (Banerjee et al., 2023), dioxidovanadium(V) Schiff base complexes ([VVO<sub>2</sub>(HL)] where HL<sub>2</sub> is an ONO Schiff base ligand) (Rana et al., 2025); oxidovanadium(V) complexes, (HNEt<sub>3</sub>)[VVO<sub>2</sub>L] and [(VVOL)<sub>2</sub>-O], with tridentate Schiff base ligand H<sub>2</sub>L [H<sub>2</sub>L = 4-((E)-(2-hydroxy-5-nitrophenylimino)-methyl)benzene-1,3-diol] (Sahu et al., 2021); and a review of describing V-complexes with ligands existing in the biosphere (Bera et al., 2025). Unlike most of these vanadium compounds with reported anticancer activity, the vanadium in our complexes is in oxidation V. However, the two vanadium(V) Schiff base complexes listed above show effects on the human cervical cancer cell line HeLa and are significantly more stable than the very reactive non-innocent vanadium Schiff base catecholate complexes that we have been designing for intratumoral administration (Levina et al., 2020; Levina et al., 2022).

Our main design criterion for a desirable antiproliferative complex to be administered intratumorally is that they must quickly decompose (Crans et al., 2004) and the decomposition products are less toxic once they have reacted and killed the tumor tissue in the cancer cells (Figure 4A) (Bates et al., 2025). We have found that the intact vanadium(V) Schiff base catecholate complex [VO(HSHED)(DTB)] is 12 times more potent than cisplatin in the T98G cell lines (glioblastoma, Figure 4B) (Levina et al., 2020). In addition, the data showed that the complex was also more toxic than in non-cancer and normal human cell lines such as HFF-1 (Figure 4B) (Levina et al., 2020). However, as shown in Figure 4B these complexes show antiproliferative effects against several other cancer cell lines including breast (MDA-MB-231), pancreatic (PANC-1) and lung (A549) cancers. Previously, the proliferative effects of this complex were reported in bone cancer cells (human chondrosarcoma, SW11353 cells) (Levina et al., 2020). The aged ligands and vanadate had a weaker effect than the intact complex. Comparing fresh solutions with aged solutions was used to compare the intact complex and free ligands/vanadate

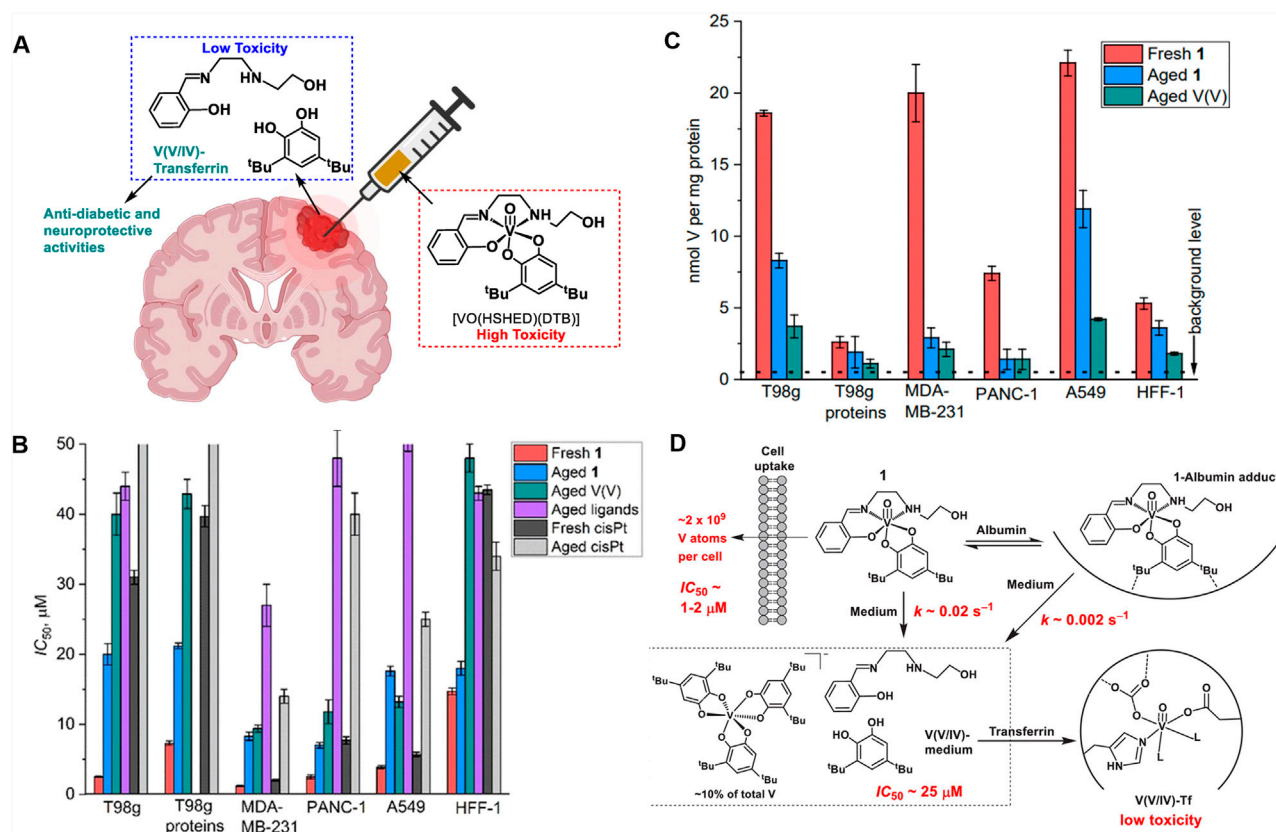


FIGURE 4

(A) Illustration of the intratumoral drug administration and decomposition into components; (B) the effects of fresh intact complex **[VO(HSHED)(DTB)]** (red; referred to a **1** in 4B and 4C), the effects of aged **[VO(HSHED)(DTB)]** hydrolyzed into vanadate, and ligands (coral blue); the effect of aged vanadate (turquoise); aged Schiff base and catechol (purple); fresh cisPt abbreviation for cisplatin (black) and aged cisPt (grey); (C) mmol of V per mg of protein and (D) proposed action of the **[VO(HSHED)(DTB)]**; the complex binds to serum albumin extending its life-time before decomposition; the complex hydrolyzes to form vanadate, ligands, and the proposed **[V(DTB)<sub>3</sub>]**; finally transferrin binds the vanadate that is formed upon hydrolysis.

and potential reaction products after the hydrolysis and redox chemistry that take place under the assay conditions. In Figure 4C, the V-uptake in cells was more after treatment by fresh **[VO(HSHED)(DTB)]** compared to treatment with decomposed and aged **[VO(HSHED)(DTB)]**, which documented that the intact complex is much more effective in entering the cell. Measuring aged solutions in addition to measure the components of the complex it also measure products that forms in the assay during the hydrolysis.

We have used the structure-activity relationship to develop more stable and potent antiproliferative complexes, all of which contained sterically hindered catecholates (Kostenkova et al., 2023; Murakami et al., 2022; Haase et al., 2024). Similarly, with structural modification of the Schiff base framework, we have been able to develop complexes with increased stability, resulting in additional potent antiproliferative agents (Bates et al., 2025). When compounds in this class of complexes hydrolyze rapidly, they show similar activity to vanadate (Kostenkova et al., 2023; Murakami et al., 2022; Haase et al., 2024). Importantly, other vanadium compounds have antiproliferative activity against glioblastoma T98G cells, as demonstrated by the hydroxyquinoline vanadium complexes, which are also active against *Trypanosoma cruzi*

(Levina et al., 2024). These compounds do not react quickly with the tumors and form more toxic side products, so although they are antiproliferative agents, they are not well suited for intratumoral administration.

Serum albumin has been reported to enhance other drugs' efficacies and has even been included in some formulations of drugs in the clinic (Kratz and Elsadek, 2012; Stukan et al., 2025; Gao et al., 2024). The presence of serum albumin in the media when treating triple-negative human breast cancer (MDAMB-231) cells with **[VO(HSHED)(cat)]** did not change the complex's antiproliferative effects (Levina et al., 2023). These observations are consistent with the expectation that when the vanadium(V) Schiff base catecholate complex hydrolyzes to form vanadate, such as reported for **[VO(HSHED)(cat)]**, the vanadium complex does not interact with serum albumin (Levina et al., 2023). In contrast, more stable and effective vanadium(V) Schiff base catecholate complexes, which contained sterically hindered substituents on the catechol such as two t-butyl groups or three i-propyl groups, were found to form an adduct with serum albumin (Levina et al., 2023). These observations were supported by UV-vis spectroscopy, demonstrating that a new species was formed in the presence of **[VO(HSHED)(DTB)]** but not in the presence of **[VO(HSHED)(cat)]**.

Finally, **Figure 4D** shows proposed pathways which the [VO(HSHED)(DTB)] complex engage in when treating cancer cells under cell culture conditions based on the experiments reported. It shows the superior cellular uptake of the intact complex, and its interaction with serum albumin that result in stabilization of the complex. The figure also illustrates that upon decomposition the components formed are less toxic, and that the V-atom is bound to transferrin as well as forming a new complex [V(DTB)<sub>3</sub>].

Although intratumoral injections (ITI) are mainly used for palliative care at this time, clinical trials involving intratumoral injections with cisplatin, oxaliplatin, and carboplatin have (Levina et al., 2022) increased by a factor of 5 since 2022 (Bates et al., 2025). In addition, the FDA has approved the use of an oncolytic virus (T-VEC), administered by intratumoral injection to treat unresectable metastatic melanoma (Hamid et al., 2020). Furthermore, similar techniques have been successfully utilized such as convection enhanced delivery (CED), which are intracranial injections of drugs designed to bypass the blood brain barrier, and has been used for the treatment of malignant gliomas (D'Amico et al., 2021; Nwagwu et al., 2021; Kang and Desjardins, 2022). Pressurized intraperitoneal aerosolized chemotherapy (PIPAC) is another administration method under development for treatment of metastatic cancers of the digestive system (Alyami et al., 2019; De Jong et al., 2021). These reports underline the fact that while currently intratumoral procedures are not routine, this method is likely to be much more accessible for cancer treatment in the future. Therefore, it is important to recognize that while novel administration strategies may differ from those more commonly used at the present time they should not be disregarded but further developed for future use. In summary, these results suggest that drugs delivered by intratumoral injections could be effective if they were reactive and immediately destroy tumor cells forming non-toxic compounds in the process and leaving healthy cells unharmed.

## Summary

Currently there are only a few metal-based therapeutics approved for and used in the clinic, whereas there are many metal-based diagnostics. Therapeutic and diagnostic drugs share many similarities regarding their pharmacokinetic properties, as upon administration they both must be distributed, taken up into the cells, and excreted properly. However, diagnostic agents and therapeutics differ drastically in their metabolism and their excretion. *In vivo* diagnostic drugs have been developed to be stable and undergo minimal metabolism, whereas therapeutic agents are designed with a particular target and often are administered as prodrugs, where some metabolism is required for action. In the case of intratumoral agents this is particularly important because they must react immediately with the tumor and upon killing the cancer cells, form non-toxic products. Metal-based radiotheranostic agents are particularly interesting because they, similarly to diagnostic agents, must be exceedingly stable and resist metabolism. This is contrary to typical therapeutics, which are administered as prodrugs and are metabolized in the cell, whereupon they interact with the target potential proteins and other targets. Indeed, as an example, <sup>64/67</sup>Cu-SAR-bisPSMA contains both the stable metal radiotracer complex as

well as the peptide ligand associated with the target receptor. However, successful development of such agents involves more elaborate ligand design as evidenced by the structure of <sup>64/67</sup>Cu-SAR-bisPSMA shown in **Figure 3**. Importantly, these agents do not comply with the guidelines for traditional drugs as defined by Lipinski, re-emphasizing that such compliance is not a requirement for successful future drugs such as in theranostic agents and drugs designed for unconventional administration strategies such as intratumoral injections.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

AM: Conceptualization, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review and editing. DC: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review and editing.

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## Conflict of interest

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## Glossary

<b>ADME</b>	Administration, Distribution, Metabolism, Excretion	<b>Y</b>	Yttrium
<b>Au</b>	Gold	<b>Zr</b>	Zirconium
<b>cat</b>	Catecholate		
<b>CED</b>	Convection Enhanced Delivery		
<b>CNS</b>	Central Nervous System		
<b>Cu</b>	Copper		
<b>CXCR4</b>	C-X-C Chemokine Receptor 4		
<b>Da</b>	Daltons		
<b>DNA</b>	Deoxyribonucleic Acid		
<b>DOTA</b>	(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)		
<b>DTB</b>	Di-tert-butyl		
<b>DTPA</b>	Diethylenetriamine Pentaacetate		
<b>FAP</b>	Fibroblast Activation Protein- $\alpha$		
<b>FAPI</b>	Fibroblast Activation Protein- $\alpha$ Inhibitor		
<b>FDA</b>	Federal Drug Administration		
<b>FDG</b>	Fluorodeoxyglucose		
<b>Ga</b>	Gallium		
<b>GBCA</b>	Gadolinium-based Contrast Agent		
<b>Gd</b>	Gadolinium		
<b>ITI</b>	intratumoral injection		
<b>Lu</b>	Lutetium		
<b>mAb</b>	Monoclonal Antibody		
<b>Mo</b>	Molybdenum		
<b>MRI</b>	Magnetic Resonance Imaging		
<b>NET</b>	Neuroendocrine Tumor		
<b>NSF</b>	Nephrogenic Systemic Fibrosis		
<b>PET</b>	Positron Emission Tomography		
<b>PIPAC</b>	Pressurized Intraperitoneal Aerosolized Chemotherapy		
<b>PSMA</b>	Prostate-Specific Membrane Antigen		
<b>Pt</b>	Platinum		
<b>r<sub>1</sub></b>	Longitudinal Relaxivity		
<b>r<sub>2</sub></b>	Transverse Relaxivity		
<b>Ru</b>	Ruthenium		
<b>SAR</b>	Sarcophagine		
<b>SPECT</b>	Single-Photon Emission Computed Tomography		
<b>SPION</b>	Superparamagnetic Iron Oxide Nanoparticle		
<b>T<sub>1</sub></b>	Longitudinal Relaxation Time		
<b>T<sub>2</sub></b>	Transverse Relaxation Time		
<b>Tc</b>	Technetium		
<b>UV-vis</b>	Ultraviolet-visible		
<b>V</b>	Vanadium		