

What is the Reason That the Pharmacological Future of Chemotherapeutics in the Treatment of Lung Cancer Could Be Most Closely Related to Nanostructures? Platinum Drugs in Therapy of Non-Small and Small Cell Lung Cancer and Their Unexpected, Possible Interactions. The Review

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Abstract: Over the course of several decades, anticancer treatment with chemotherapy drugs for lung cancer has not changed significantly. Unfortunately, this treatment prolongs the patient's life only by a few months, causing many side effects in the human body. It has also been proven that drugs such as Cisplatin, Carboplatin, Oxaliplatin and others can react with other substances containing an aromatic ring in which the nitrogen atom has a free electron group in its structure. Thus, such structures may have a competitive effect on the nucleobases of DNA. Therefore, scientists are looking not only for new drugs, but also for new alternative ways of delivering the drug to the cancer site. Nanotechnology seems to be a great hope in this matter. Creating a new nanomedicine would reduce the dose of the drug to an absolute minimum, and thus limit the toxic effect of the drug; it would allow for the exclusion of interactions with competitive compounds with a structure similar to nucleobases; it would also permit using the so-called targeted treatment and bypassing healthy cells; it would allow for the introduction of other treatment options, such as radiotherapy directly to the cancer site; and it would provide diagnostic possibilities. This article is a review that aims to systematize the knowledge regarding the anticancer treatment of lung cancer, but not only. It shows the clear possibility of interactions of chemotherapeutics with compounds competitive to the nitrogenous bases of DNA. It also shows the possibilities of using nanostructures as potential Platinum drug carriers, and proves that nanomedicine can easily become a new medicinal product in personalized medicine.

Keywords: fullerenes, nanotube, nanoparticles, drug delivery, personalized medicine, platinum-based drugs, cisplatin, carboplatin, oxaliplatin, nedaplatin

Introduction

Cancer is defined by the WHO (World Health Organization) as a group of diseases caused by abnormal, uncontrolled cell growth, which can be located in almost any organ or tissue of the body.¹ The primary cause of cancer-related deaths is metastasizing,²⁻⁷ which is the spread of cancer cells from the initial organ or tissue to another one in the host.⁷

Nowadays, cancer is one of the leading causes of death globally. The most common women's cancers are breast, colorectal, lung, cervical, and thyroid, whereas among men, these are lung, prostate, colorectal, stomach, and liver cancers.¹

Lung cancer is one of the most common and serious types of cancer worldwide, for which detailed treatment regimens are presented. In 2022, lung cancer had the most new cases among all cancers, as many as almost 2.5 million, which constituted 12.4% of all new cancer cases. Although this statistic was comparable to breast cancer, lung cancer had



a twice as high mortality rate of over 1.8 million people, which accounted for 18.7% of all cancer deaths.⁸ The situation in Poland in 2019 is similar: among men it accounted for 16.1% and among women for 9.9% of new cases, while the mortality statistics were 27.4% and 17.9%, respectively.⁹ According to the American Cancer Society's estimates of lung cancer in the USA, in 2024 there will be over 230 thousand new cases and over 125 thousand deaths.¹⁰

Lung cancer can be divided into two histologically different classes that grow and spread differently,¹¹ Small Cell Lung Cancers (SCLC) and Non-Small Cell Lung Cancer (NSCLC).

Small Cell Lung Cancers (SCLC) - they constitute approximately 10–15% of all lung cancers. SCLC originate from hormonal cells of the lung and are characterized by rapid growth, a tendency to metastasize (even in over 60% of patients¹²), and susceptibility to chemotherapy. The survival rate is extremely low for 5 years - only 7%.¹³ Fortunately, they are highly susceptible to chemotherapy.¹² Most often, they are located centrally in the lungs, and their presence is related to smoking.¹⁴

Non-Small Cell Lung Cancer (NSCLC) - they constitute approximately 80% of all lung cancers, and unlike SCLC, they most often develop slowly and may remain hidden until an advanced stage. They can originate from different types of cells.¹⁴ Non-Small Cell Lung Cancer (NSCLC) being divided into many types, the most common of which are squamous cell lung cancer, large cell lung cancer, and adenoma. Active and passive smoking are factors that increase the risk of developing the disease, but NSCLC can be detected in people who have never smoked. Unfortunately, NSCLC is more resistant to chemotherapy and radiotherapy than SCLC.¹⁰ The survival rate for the next 5 years is significantly higher - 30%.¹⁰

The likelihood of effective treatment increases with the early detection of cancer.^{11,15,16} The treatment method depends on the type of cancer cells, their location, and the stage of the disease. Nowadays, traditional therapeutic treatment methods include, first of all, surgical resection, radiation therapy, and chemotherapy, while newer forms of treatment include targeted therapy, immunotherapy, hormone therapy, gene therapy, and photodynamic therapy.^{3,11,17–20} Currently, however, combined therapy is used more and more often instead of monotherapy (Chapter 2, Subsection 2.4). The combination chemotherapy, including a Platinum derivative and drugs from other groups, is used in the treatment of many cancers (Chapter 2, Subsection 2.4 and [Supplementary Materials: Tables S1 and S2](#)). Nowadays, scientists are constantly looking for new anticancer drugs (Chapter 4, Subsections 4.3–4.5) that would provide a better therapeutic effect with minimal side effects (Chapter 2, Subsection 2.3), but also for new forms of treatment, which includes the creation of nanomedicine (Chapter 4). A significant development in chemotherapy is the combination of nanostructures with Platinum-derivative drugs (Chapter 4), which improves drug accumulation at the target site and weakens their side effects. Moreover, the creation of nanomedicine limits to an absolute minimum the possibility of combining the Platinum compounds with amino acids in the peripheral blood (Chapter 3, Subsection 3.2). Going further, at the cellular level, it limits the combination with compounds competing with nucleobases (Chapter 3, Subsection 3.1). There are many examples of combining a nanostructure with a chemotherapeutic agent in the literature (Chapter 4). Platinum compounds are often combined with organic nanostructures (protein nanotubes, liposomes, nanobodies, polymers), inorganic nanostructures (dendrimers) and carbon nanostructures represented by fullerenes, nanotubes, and rhombellans (Chapter 4, Subsection 4.4).

Platinum Compounds

Platinum compounds are among the first, most effective, and most frequently used chemotherapy drugs. The oldest of them is Cisplatin (formerly Peron Salt²¹), discovered by Micheal Perone in 1844.²² However, its cell division-inhibiting properties remained hidden until 1965, when Bennett Rosenberg of the University of Michigan described the inhibition of sarcomas and leukemias in mice in the presence of Cisplatin.²³ It focused the attention of the scientific world on Platinum compounds, which naturally led to the expansion of their family to include additional substances. Currently, the family of Platinum derivatives can be divided into compounds that have been approved for treatment around the world, such as Cisplatin, Carboplatin, Oxaliplatin, and those that are only used in selected countries, such as Nedaplatin, Heptaplatin and Lobaplatin, taken by patients in Japan, Korea and China, respectively.^{24–27} Over the years, thousands of Platinum-derived compounds have been tested, but most of them were rejected in subsequent stages, mainly due to their high toxicity.²⁸

Cisplatin (used since 1978) is a drug with a very wide range of uses in solid cancers, such as testicular cancer, ovarian cancer, bladder cancer, lung cancer, head cancer, neck cancer, stomach cancer, mesothelioma, cervical cancer, prostate cancer, skin cancer, salivary gland cancer, and others ([Figure 1a](#)).

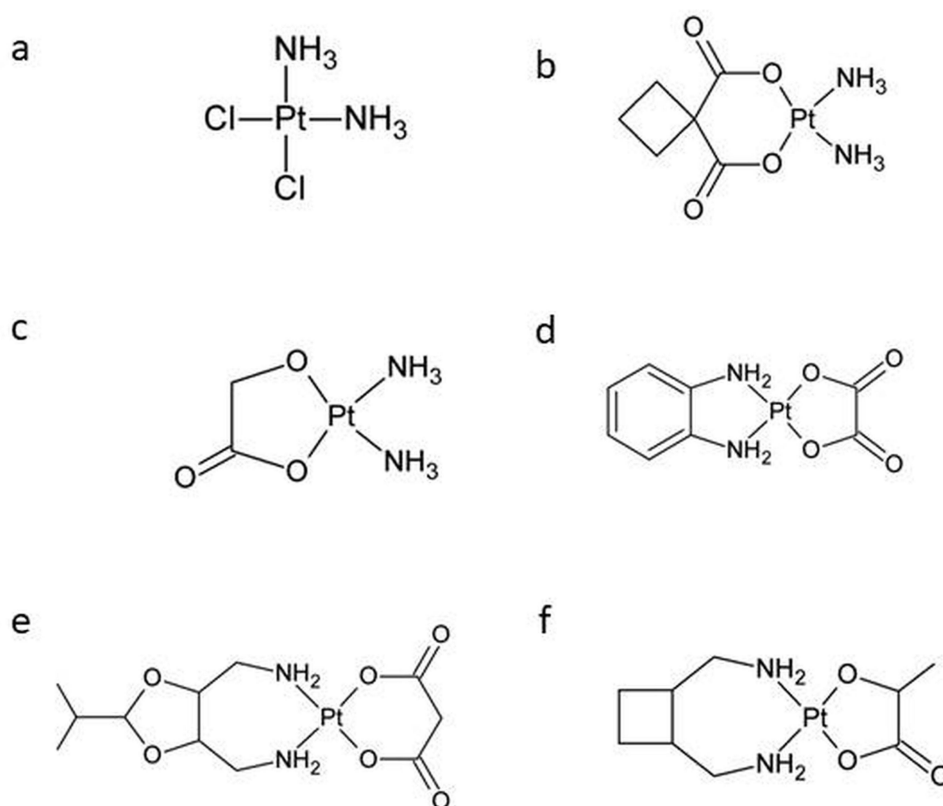


Figure 1 The structure of Pt drugs; (a) - Cisplatin, (b) - Carboplatin, (c) - Nedaplatin, (d) - Oxaliplatin, (e) - Heptaplatin, and (f) - Lobaplatin.²⁹⁻⁴⁷

Carboplatin (used since 1989) is a compound belonging to a second-generation of platinum drugs with weaker anticancer activity but, at the same time, a less destructive effect on the body, compared to cisplatin, which is used in ovarian and testicular cancers, small-molecule lung cancer, neck cancer, head cancer, bladder cancer, breast cancer, brain cancer, and neuroblastoma (Figure 1b).^{28,48-65}

Nedaplatin (used since 1995 in Japan) is a second-generation platinum drug, developed to provide a treatment with effectiveness similar to that of cisplatin and better than Carboplatin but with decreased renal and gastrointestinal toxicities. Moreover, it is much more soluble in water than Cisplatin. Nedaplatin is used to treat cancers of the head, neck, a small cell lung cancer, as well as esophagus (Figure 1c).^{28,59,60,66-71}

Oxaliplatin (used since 1996) is a third-generation platinum drug, developed to overcome the resistance against first- and second-generation platinum drugs. Oxaliplatin has a different mode of action than Cisplatin, it creates fewer cross-links, but induces ribosome biogenesis stress. The lipophilic ligand increases penetration through cell membranes. It is a substance used mainly in chemotherapy of the colorectal cancer and, to a lesser extent, in stomach and esophageal cancers (Figure 1d).^{42,58-60,65,72-110}

Heptaplatin (used since 1999 in Korea) is currently used in the treatment of gastric cancer and has fewer hematologic toxicities than Cisplatin with this same combination. The important advantage is its high solubility in water (Figure 1e).^{59,111-114}

Lobaplatin (used since 2010 in China)^{24,25,115-117} is used in patients suffering from chronic myelogenous leukemia, small cell lung cancer and metastatic breast cancer¹¹⁸ (Figure 1f).^{25-27,59,66,115-118}

All the above-mentioned compounds are administered in monotherapy or combined therapy, in which, in addition to Platinum derivatives, other medicinal substances are used, and each one has its own patterns (Table S1 given in Supplementary Materials). In this work, we will focus mainly on complex therapies for Non-small cell lung cancer^{15,16} and Small cell lung cancer^{119,120} (Chapter 2, Subsection 2.4 and Table S2 given in Supplementary Materials).

The development strategies for these drugs focus on the combination therapy mentioned above (given in [Supplementary Materials](#)) and the therapy using nanostructures (for drug delivery), as well as other key issues: low selectivity towards cancer cells, limiting the phenomenon of resistance, and toxicity of chemotherapy.

Mode of Actions

Platinum compounds are administered intravenously in the form of a saline solution in specially prepared bags, to which a colored infusion device is connected. The bag contains all the necessary drug data (name, active substance, dose, solvent, infusion time), as well as the patient's data and information to protect it from light. These solutions contain Platinum compounds in the form of a prodrug, which, due to the high concentration of chloride ions in the blood, remains inactive, but this state changes after the drug enters the cell.⁴⁰ Compounds derived from Platinum penetrate the cell membrane by passive diffusion or active transport via the copper transporter CTR1¹⁰⁶ organic cation transporters (OCTs),¹²¹ solute carriers (SLCs)¹²¹ and ATP-binding cassette (ABC) multidrug transporters.¹²¹ The details on these mechanisms for each Platinum drug are given in [Table 1](#).

The choice of transport type depends on lipophilicity. More lipophilic substances, such as Oxaliplatin, will have dominant passive transport, whereas more hydrophilic substances, such as Heptaplatin and Nedaplatin, will cross copper receptors to a greater extent ([Figure 2](#) and [Table 1](#)).

After passing through the membrane, these compounds are inactivated during the hydrolysis process and then show significant affinity for proteins (cysteine sulfhydryl groups)^{47,125–133} and nucleic acids (nitrogen atoms of purines, ie guanine and adenine).^{25,33,34,66,117,134,135} As a result of their action on DNA, the compounds generate a huge number of cross-links in nucleic acids, both within the same DNA strand and between strands, which distorts and damages the DNA. If these changes are not repaired by DNA polymerase, it leads to apoptosis ([Figure 3](#)).^{136–139}

The most preferred attachment site for Cisplatin is the N7 nitrogen atom in the nitrogenous base of guanine ([Figure 4](#)). Additionally, the N7 of adenine, N3 of cytosine and thymine, and N1 of guanine and adenine are less preferred sites. Cisplatin attaches to the greatest extent to the two guanine bases laying on the same strand. They may lie next to each other or be separated by another base.

The next most common connection is the attachment of Cisplatin to a guanine base and an adenine base, lying next to each other on the same strand. Bonds between DNA and monoadduct strands are relatively rare⁶² ([Figure 5](#)).

Additionally, Platinum drugs stimulate the production of reactive oxygen species (ROS), which indicate oxidative stress. This process is mainly responsible for drug toxicity.^{140–146} ROS also lead to cell death by damaging mitochondrial DNA, which causes mitochondrial leakage and the release of cytochrome C and caspase-9, which initiate the apoptotic pathway.¹³⁵

Table 1 Mechanism of Platinum Drug Transport Across the Cell Membrane

Cisplatin	Passive diffusion is believed to play a major role in Cisplatin accumulation. ⁴¹ However, active transport, although not so significant, also occurs using, among others, copper transporters, ¹²² organic cation transporters and the family of multidrug and toxin extrusion ¹²³ .
Carboplatin	Carboplatin is transfused through the cell membrane by passive diffusion, although it can enter the cell through active transport (copper transporters). ¹²⁴ In contrast to cisplatin, as research has shown, it is not transported by organic cation transporters and multidrug and toxin extrusion family. ¹²³
Oxaliplatin	In the case of Oxaliplatin, passive transport predominates initially after administration, but over time, active transport begins to dominate. The main types of transporters include organic cation transporters and multidrug and toxin extrusion family. ^{105,123}
Nedaplatin	The transport mechanism of Nedaplatin is still little known, but we do know that organic cation transporters and multidrug and toxin extrusion family transporters are not involved in it. ¹²³
Heptaplatin	Not documented. ⁶⁶
Lobaplatin	Not documented. ⁶⁶

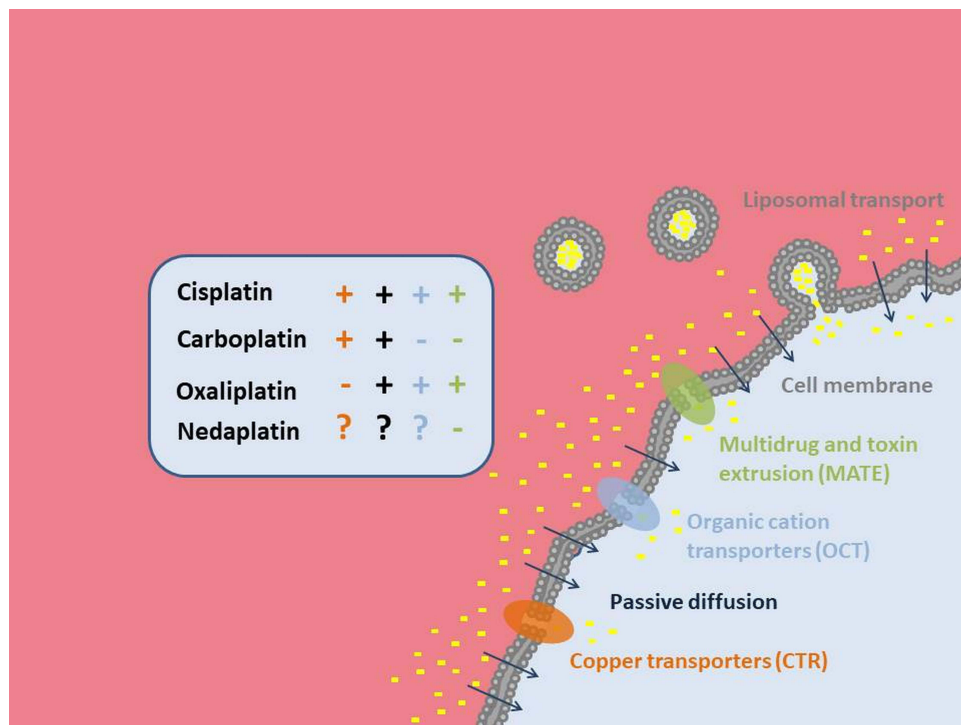


Figure 2 Types of transport of chemotherapy drugs across the cell membrane and the blood/cancer cell barrier. Symbols +, -, and ? denote activity, inactivity, and no data in the literature, respectively.^{25,33,34,47,66,117,125-135}

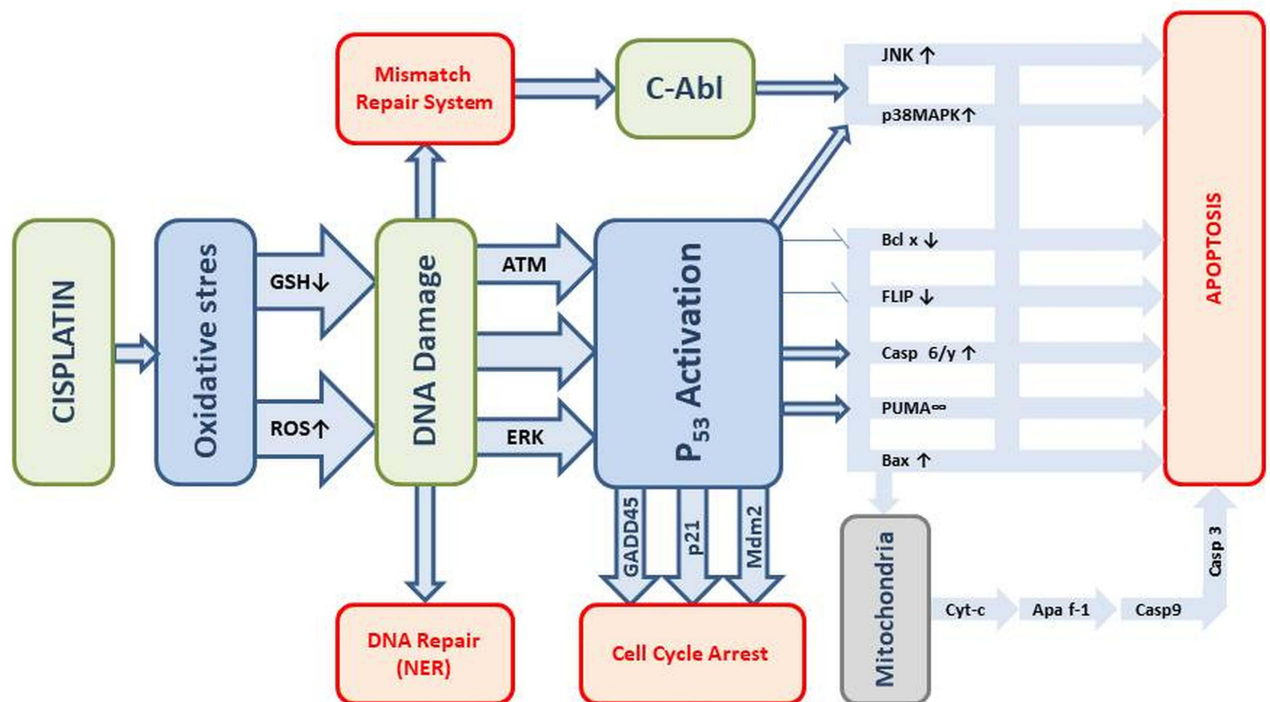


Figure 3 The scheme of the mode of action of Cisplatin.^{123,136-139}

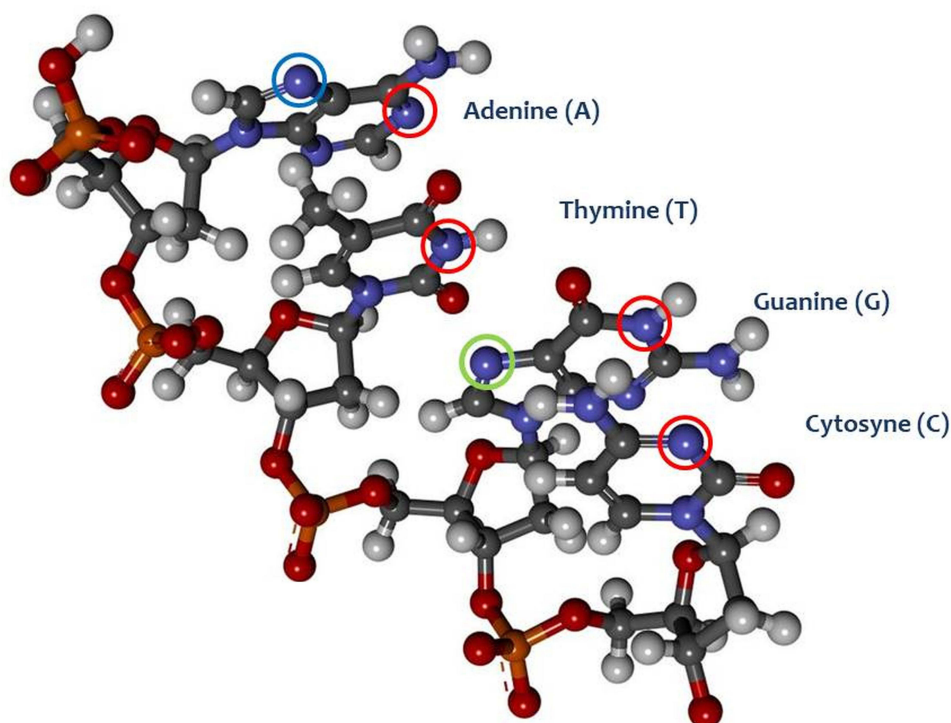


Figure 4 Binding sites of Cisplatin with nucleobases of DNA.^{40,62}

Resistance

One of the most important reasons why the treatment with Platinum derivatives is abandoned or does not bring the expected results is the phenomenon of resistance. This phenomenon makes further treatment, eg with Cisplatin, ineffective and another effective therapy must be found. Such a solution may be, for example, the use of another Platinum-derivative drug, eg Nedaplatin, to which cancer cells are not resistant.⁶⁷ Resistance to Platinum compounds can be divided into three types: pre-target, on-target and post-target. Pre-target resistance involves at least two processes. The first one involves reducing the cellular accumulation of Platinum-derivative drugs. This process occurs, for example, by reducing the absorption of Platinum-derivative drugs, eg by affecting copper transporters¹⁴⁷ or also by increasing efflux from cells.¹⁴⁸ The second one involves increasing the deactivation of Platinum during its journey to the cell and in the cell by binding it to other substances, such as B vitamins or proteins containing sulfur amino acids.¹⁴⁸ As for the on-target resistance, cells acquire greater resistance to the action of Platinum-derivative drugs by improving the repair processes using DNA polymerase, which cuts out the nucleotide attacked by drugs. As a result, the changes caused by Platinum-derivative drugs that were supposed to lead to apoptosis are repaired, and the cell does not start the process of apoptosis.^{33,134} Post-target resistance to Platinum-derived drugs may involve inhibition of the reaction cascade leading to apoptosis. One of the most common examples of such resistance is TP53 inactivation, which occurs in approximately half of all human cancers.¹⁴⁹ Unfortunately, the resistance that develops is most often multifactorial in nature, and therefore stopping one pathway of resistance development cannot bring any clear benefits. Additionally, the very low selectivity of Platinum-derivative drugs, and therefore the high administered dose, drives the development of resistance. This effect also increases with the administration of subsequent doses.¹⁵⁰

Side Effects

The second most common reason that causes the treatment with Platinum derivatives to be discontinued is the resulting side effects. All Platinum-based drugs have dozens of different side effects, which are depicted in Figure 6. Their main reason is the poor selectivity of Platinum compounds. This means that apoptosis is not only induced in cancer cells but also in healthy ones.^{50,56,64,69,73,83,87,90,92,110,111,151–162} Each Platinum derivative has its own side effects, which occur

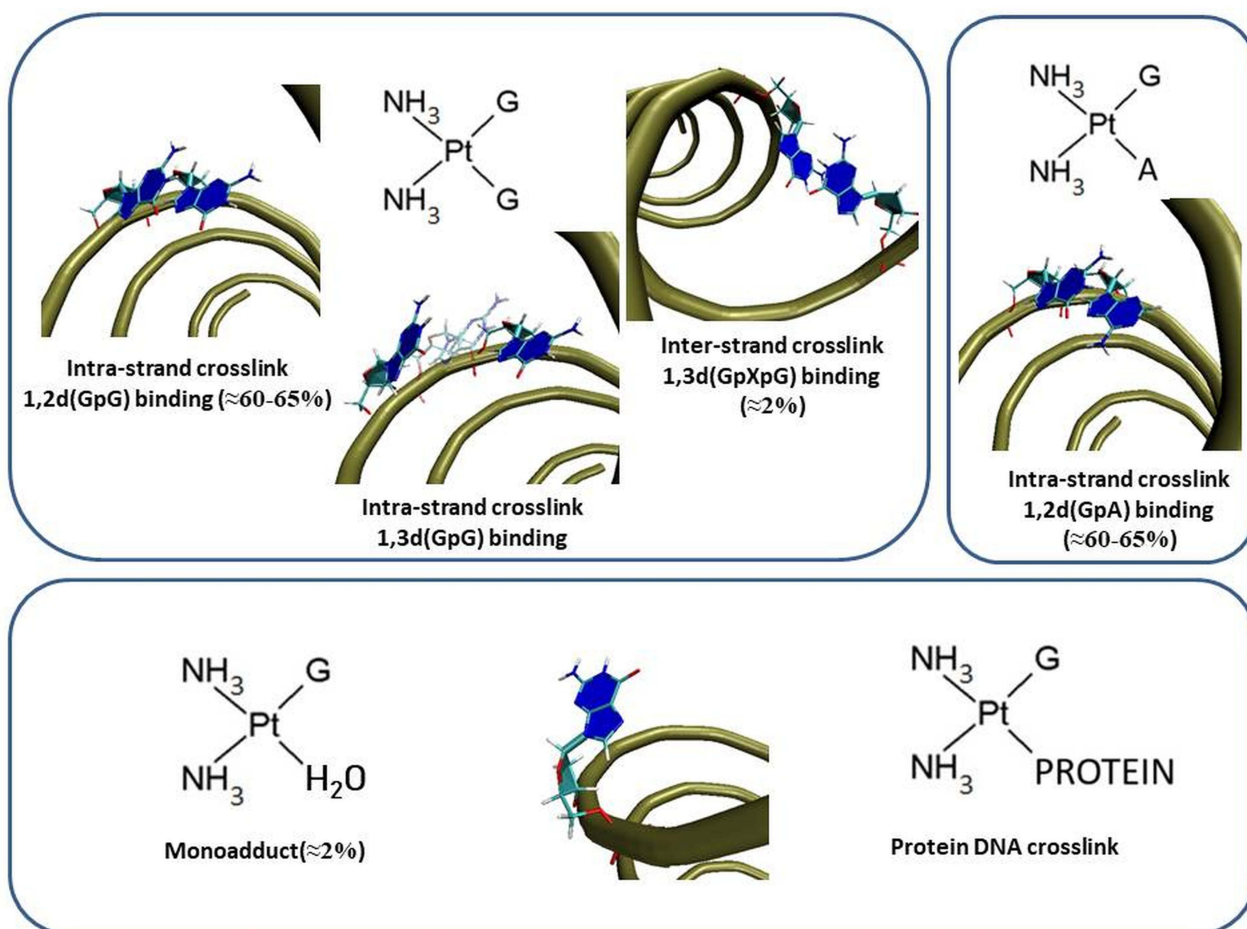


Figure 5 Intra- and inter-strand cross-linking of Platinum-derivative drugs with DNA bases.

relatively frequently after its use and are presented in Table 2. Side effects may become so intense that they require us to limit the dose of the drug or generally discontinue the treatment with a given substance. For Cisplatin, the most common limiting effect is nephrotoxicity, for Carboplatin it is myelosuppression, and for Oxaliplatin it is neurotoxicity.¹⁵⁴

One of the most common side effects is gastrointestinal toxicity. The effect on the digestive system includes, in addition to the most common nausea, vomiting, reflux, diarrhea, and constipation, also gastrointestinal disorders, and, even though relatively rarely, it may lead to eating disorders. Platinum compounds release 5-hydroxytryptamine into the gut, which induces vomiting. Additionally, consequences may damage the villus.³² The effect of Platinum compounds on the bone marrow causes hematological toxicities such as leukopenia (low level of white platelets), especially neutropenia (low level of neutrophils), thrombocytopenia, and anemia (low level of red blood cells). The sum of all these phenomena is called myelosuppression, in which the production of all blood cells is decreased. Although this phenomenon is caused by all Platinum drugs from this group, it is most characteristic of Carboplatin for which it is a limiting factor.¹⁶⁵ What's more, for Loboplatin, the dose-limiting toxicity is thrombocytopenia.⁵⁹ Platinum compounds are mainly excreted in the urine and therefore also cause nephrotoxicity, which is mainly manifested by acute renal failure, reduced reabsorption of magnesium and calcium (which may lead to hypomagnesemia and hypokalemia), reduced synthesis of Erythropoietin (the hormone responsible for the maturation of erythrocytes), and increased levels of uric acid in the blood (hyperuricemia). Cisplatin has the highest nephrotoxicity, affecting almost 90% of patients, for whom it is a limiting factor.^{154,166} A very common complication, especially among children, is ototoxicity, damage to the inner ear which may manifest itself in pain, loss of high-frequency hearing (4000–8000 Hz), or balance disorders.^{154,161,167,168} Ototoxicity may be low in the early stages of treatment, however, with more cycles, the risk increases significantly.^{154,165} The mechanism of ototoxicity is not clear,

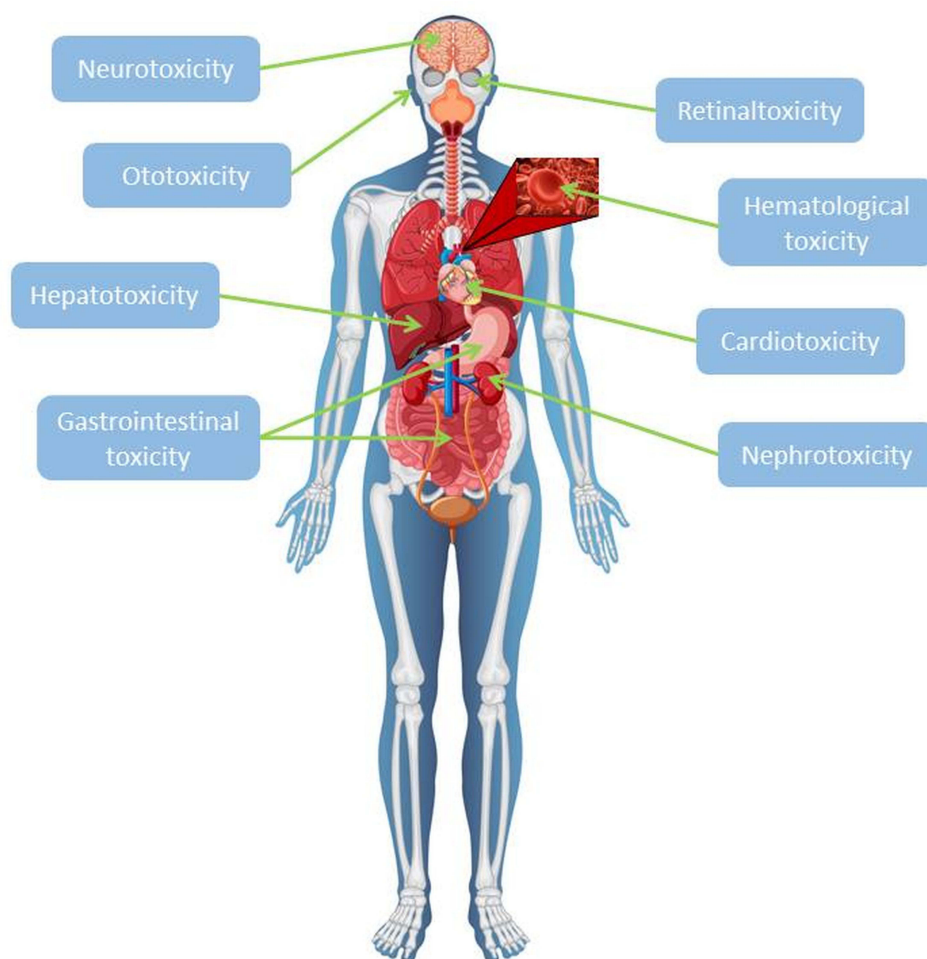


Figure 6 The side effects of Cisplatin.¹⁵⁴ This picture has been designed using assets from Freepik.com.¹⁶⁴

however it is assumed that the reason is reactive oxygen species (ROS). Platinum drugs enable the NADPH oxidase to lead ROS production.¹⁶⁷ After infusion with Platinum compounds, severe neuropathies have been observed, which may include paresthesia, areflexia, loss of proprioceptive and vibration sensations, seizures, Lhermitte's sign, and encephalopathy.¹⁶⁹ Symptoms tend to be stronger in distal parts (such as hands and feet) and the perioral and pharyngolaryngeal areas. Peripheral sensory neuropathies are correlated with an increased cumulative dose administered.¹⁷⁰ Nevertheless, an entire

Table 2 The Side Effects of Platinum Derivatives

Platinum Derivatives	The Side Effects
Cisplatin	Hematological toxicities, ³⁷ gastrointestinal toxicity, ³⁷ ototoxicity, ¹⁵⁵ nephrotoxicity, ¹⁵³ neurotoxicity, ¹⁵⁴ allergic reaction ¹⁵⁶ and hepatotoxicity ¹⁵⁷
Carboplatin	Myelosuppression, ¹⁵⁴ neurotoxicity, ¹⁵⁴ gastrointestinal toxicity, ¹⁵⁴ allergic reaction, ⁵⁰ ototoxicity, ¹⁶⁴ nephrotoxicity ⁵⁶
Oxaliplatin	Neurotoxicity, ⁹⁰ gastrointestinal toxicity, ^{64,83,158,159} hematological toxicities, ⁹⁰ nephrotoxicity, ^{87,92,160} hepatotoxicity ⁷³
Nedaplatin	Thrombocytopenia, neurotoxicity ^{68,69}
Heptaplatin	Nephrotoxicity, ¹¹² hepatotoxicity, ¹¹⁴ neurotoxicity ^{111,112}
Lobaplatin	Thrombocytopenia, gastrointestinal toxicity, neurotoxicity ⁶⁸

loss of motor function is extremely rare, and symptoms disappear after a few days and, in rare situations, last for a maximum of 4 years.¹⁵⁴ Neuropathies are the main cause of limiting Oxaliplatin usage.¹⁵⁴ Cardiotoxic effect is rarely observed and mainly manifests itself as arrhythmia, tachycardia (heart rate over 100 beats per minute) and bradycardia (heart rate under 60 beats per minute), cardiac ischemia (blood flow to your heart is reduced), myocardial infarction, diastolic disturbances of the ventricles, and pericarditis.¹⁷¹ The mechanism of action of Platinum compounds' cardiotoxicity is unknown, however there is some evidence that it is linked to ROS.¹⁷² The liver is an important organ where several biochemical processes occur, for example, the metabolism of a majority of drugs. Oxidative stress is the main reason for Platinum compounds' induced hepatotoxicity. These created ROS lead healthy liver cells to apoptosis.¹⁶² On the other hand, Cisplatin and Oxaliplatin have the ability to damage liver sinusoids (liver blood vessels). Consequently, these damages indicate liver vascular disorders.¹⁷³ Side effects may become so intense that they can require limiting the dose of the drug or generally discontinuing the treatment with a given substance. For Cisplatin, the most common limiting effect is nephrotoxicity, for Carboplatin it is myelosuppression, and for Oxaliplatin it is neurotoxicity.¹⁵⁴ To sum up, side effects may include delicate, reversible, and not very bothersome symptoms, such as hair loss,¹⁷⁴ as well as irreversible, troublesome symptoms that will reduce the quality of life and may pose a threat to health and life.

For this reason, finding a solution that will significantly increase the selectivity and thus reduce the side effects of Platinum-based drugs is such a big challenge. Scientists are trying to modify existing drugs or replace them with others with similar effects and uses.^{175–177} One of the possible modifications that Platinum compounds can undergo in order to reduce side effects is their conjugation with nanostructures.^{178–189}

General Schedules in Treatment of Lung Cancer in the Therapy with Platinum Drugs

The combination chemotherapy, including a Platinum derivative and drugs from other groups, is used in the treatment of many cancers (Table S1 and Table S2 given in Supplementary Materials). There are two main reasons for this phenomenon.

The first one is that we use different substances that produce a synergistic effect. This may be another cytostatic that acts in a different way, eg Vinorelbine, Gemcitabine, Etoposide, or immunotherapeutic drugs like a monoclonal antibody, eg Atezolizumab, Bevacizumab and Pembrolizumab. Monoclonal antibodies can act in multiple ways. One of them is to block the activity of abnormal proteins in cancer cells. The second way is to strengthen the immune system by inhibiting or stopping immune checkpoints. As a result, cancer cells cannot block these points and thus remain hidden from immune system cells. Such points include the PD-1/PD-L1 pathway^{190–194} and antibodies include Atezolizumab, Nivolumab, Pembrolizumab.¹⁹⁵

What's more, the administration of these substances helps to reduce the phenomenon of resistance to a specific drug, especially in the event of treatment relapses.²⁸ In the case of Cisplatin, the phenomenon of resistance is described as a change in cellular uptake, efflux of Cisplatin from the cell, increased detoxification of molecules in the liver, or increased DNA repair and inhibition of apoptosis.^{28,196} All this makes the therapy with a given cytostatic less effective, and it is necessary to look for another alternative to the treatment or, if possible, increase the dose of the drug, which will further increase resistance and intensify side effects. Table 3 shows a regimen consisting of Carboplatin, Paclitaxel and Pembrolizumab, which was used in Stage IV Non-Small Cell Lung Cancer with PD-L1 expression lower than 50%, without the presence of EGFR gene mutations or rearrangements of the ALK and ROS1 genes. The dose of Carboplatin depends on the glomerular filtration rate (GFR) and the formula for the dose in milligrams is expressed as $AUC \times (GFR + 25)$, dissolved in 500 mL of a 5% glucose solution. However, the dose of Paclitaxel depends on the body surface and is 200 mg for each 1 m² of the body dissolved in 500 mL of 0.9% NaCl. The monoclonal antibody Pembrolizumab has a fixed dose of 200 mg dissolved in 100 mL of 0.9% NaCl. The infusion time varies depending on the substance: Carboplatin is 1 hour, Paclitaxel is 3 hours, and Pembrolizumab is 0.5 hour. All three substances are always administered during the first day of a twenty-one-day treatment cycle. The number of repeated cycles in the treatment regimen for Carboplatin and Paclitaxel is 4 and for Pembrolizumab it is 35. However, these data may vary depending on the treatment regimens. All schemes are located in Supplementary Materials (Table S1) and a fragment of this table containing the above scheme is located below (Table 3).

Table 3 Lung Cancer Treatment Regimens.¹⁹⁷

Non-Small Cell Lung Cancer (NSCLC)				
I.	Platinum drug	Combination drugs		Types of cancer
	Carboplatin	Paclitaxel	Pembrolizumab	Non-Small Cell Lung Cancer (NSCLC) Stage IV (cancer has spread from its original location to distant parts of the body), with PD-L1 expression lower than 50%, without the presence of EGFR gene mutations and rearrangements of ALK and ROS1 genes.
		Tubulin-targeted cytostatic drug	Monoclonal antibody, targets the programmed cell death protein 1 (PD-1) receptor of lymphocytes	
Dosage				
	AUC 6 (*Carboplatin Dose [mg] = target AUC x (GFR+25))	200 mg/m ²	200 mg	
Diluent				Number of cycles
	5% Glucose, 500 mL	0,9% NaCl, 500 mL	0,9% NaCl, 100 mL	Carboplatin and Paclitaxel 4 cycles, Pembrolizumab 35 cycles
Time				Cycle length
	1h	3h	30min	21 days
Days of therapy				
	1st day of cycle	1st day of cycle	1st day of cycle	

Structures Competitive to Nucleobases of DNA

The mechanisms of action of Platinum-derived compounds have low selectivity, which makes them react with many different compounds. Based on in silico and experimental studies, it has been proven that Platinum-derived drugs can easily react and form complexes with other chemical compounds containing aromatic rings, especially nitrogen or sulfur, with a lone pair of electrons.^{58,102,198–200}

B Vitamins

One of such groups are B vitamins, ie a group of eight water-soluble vitamins (B1, B2, B3, B5, B6, B7, B9, and B12), which play the role of cofactors for many cellular metabolic pathways and enzymes involved in the synthesis of nucleic acids.^{201–220} Only 5 out of the 8 are similar to purines, owing to the fact that these vitamins contain aromatic rings with a nitrogen atom (B1, B2, B3, B6, and B9). Based on in silico studies, it has been proven that Platinum-derivative drugs can easily react and form complexes with other chemical compounds with a structure similar to nucleobases.^{57,102,198–200} Such compounds include B vitamins, which can clearly compete with the nitrogenous bases of DNA.^{57,102,199,200} Ab initio research has been confirmed by experimental research.⁵⁷ Physico-chemical characterization of interaction between vitamins and Platinum drugs was performed using UV-vis spectroscopic techniques.⁵⁷

Thiamine (vitamin B1) is a coenzyme in the metabolism of carbohydrates, and additionally influences the synthesis of the neurotransmitter gamma-aminobutyric acid and catalyzes the conversion of pyruvate to acetyl-CoA. Deficiency may lead to disorders of the nervous system (beriberi disease), heart muscle, and skeletal muscles, as well as cardiovascular disorders.^{201,202,212,213,221–223} Riboflavin (vitamin B2) takes part in tissue respiration processes and is a component of many oxidation-reduction enzymes. Additionally, the vitamin takes part in the metabolism of carbohydrates, fats, and proteins, catalyzing oxidation processes. Deficiency may cause disorders in the functioning of the nervous system and inflammation of the mucous membranes.^{201,202,215,216,224} Niacin (vitamin B3) participates in the transfer of hydrogen and electrons in the processes of cellular respiration, glycolysis and lipid biosynthesis. Moreover, it is necessary for the proper functioning of the brain and the peripheral nervous system, and is also involved in the synthesis of the sex

hormones, cortisol, thyroxine, and insulin. Deficiency may lead to pellagra, disorders of the nervous system, and the glycolysis process.^{201,202,217–219} Vitamin B6 is a group of six chemically similar compounds that can transform into each other and have a common active form, pyridoxal 5'-phosphate. This form is an extremely important cofactor in the metabolism of complex carbohydrates, fatty acids, phospholipids and cholesterol.^{201–204,220} It is also involved in heme synthesis.^{201,202,205,225} Vitamin B6 deficiencies cause inflammation of the skin and mucous membranes, neuropathies, and anemia.²¹⁰ These vitamins are of key importance, eg in certain disease states like diabetes and Wernicke's encephalopathy.^{206–208,211} However, it is worth noting and emphasizing that neuropathies are a common side effect of Platinum.^{209,212} It has been proven that B vitamins can weaken the effect of Platinum-derivative drugs.^{57,102,198–200}

Based on previous research, it can be concluded that niacin (vitamin B3) has the greatest affinity for Cisplatin, both for its mono- and diaqua²⁰⁰ forms (Figure 7). In the case of thiamine (vitamin B1), Cisplatin forms complexes more easily with the nitrogen atom in the N1 position in the ring than with the N7 atom. Pyridoxal phosphate (vitamin B6) has a similar ease of complex formation as thiamine.²⁰⁰ On the other hand, the behavior of riboflavin (vitamin B2) is completely different.²⁰⁰ This vitamin reacts poorly with Carboplatin. A spontaneous reaction can be observed for pyridoxal phosphate (vitamin B6) and the value of Gibbs free energy of reaction, ΔG_r , is negative. Niacin (vitamin B3) forms much worse complexes with Carboplatin,⁵⁷ where the value of ΔG_r is approximately zero. Oxaliplatin has the same affinity for B vitamins as Cisplatin.¹⁰² However, changing the calculation level from B3LYP/6-31G(d,p)/LANL2DZ²²⁶ to MN15/def2-TZVP changes this picture.¹⁰² The most reactive vitamins are thiamine (vitamin B1) and pyridoxal phosphate (vitamin B6), and the least reactive one is niacin (vitamin B3).

This means that a specially calculated therapy cannot be as effective as it could be expected, because some of the drug can react with vitamins instead of purines in DNA. This highlights another important problem, which is that a Platinum-derivative drug may react with competing molecules other than nucleobases before it reaches the target site, ie tumor DNA.

Proteins

Another group that may react with Platinum-derivative drugs are proteins.^{31,152,227–229} The main binding sites are sulfur-containing amino acids, such as methionine and histidine. Nitrogen atoms located on Lysine amino acids are also the site

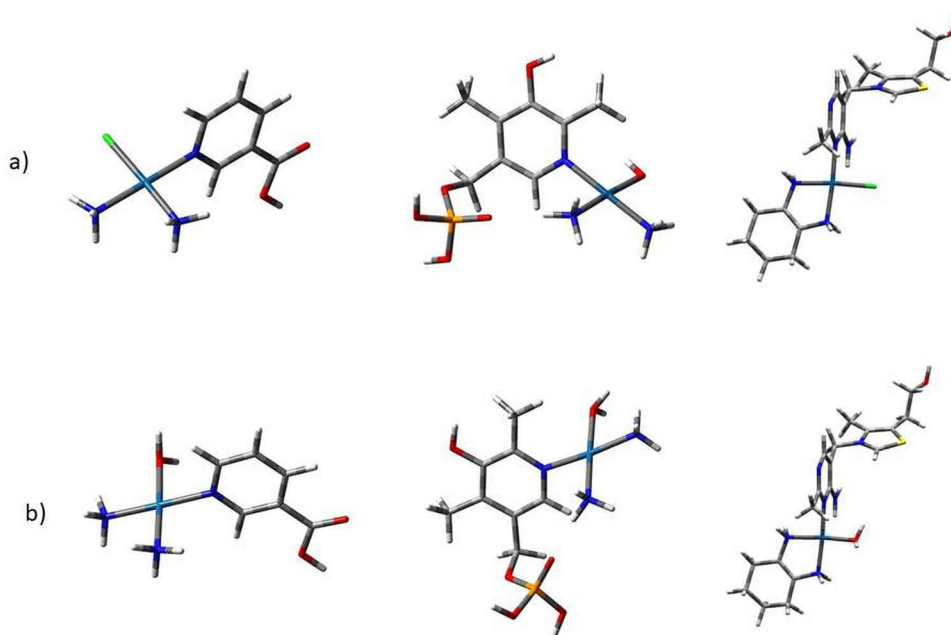


Figure 7 Exemplary structures of mono (a) and diaqua (b) complexes of Cisplatin with niacin (vitamin B3), Carboplatin with pyridoxal phosphate (vitamin B6) and Oxaliplatin with thiamine (vitamin B1).^{57,102,198,199}

of binding to Platinum-derived drugs. Proteins can form adducts with more than one Pt-containing fragment or coordinating protein, and the number of bounds increases with time.^{31,152,227–229}

Cisplatin, Carboplatin and Oxaliplatin were tested in this context, and the studies proved that they bind to proteins, mainly albumin, in the bloodstream by 98%, 25%, and 98%, respectively. Of which, 98% of the administered cisplatin and 87% of Oxaliplatin were irreversibly bound to proteins. This means that cisplatin binds practically irreversibly to proteins, while Oxaliplatin binds mostly irreversibly. However, in the case of Carboplatin, only 10% of the administered dose binds irreversibly, which means that if Carboplatin is already bound to proteins, it binds mainly reversibly.²³⁰

Other Structures

Drugs containing Platinum, due to their low selectivity towards nucleic acids, may interact with numerous other structures that contain a nitrogen or sulfur atom with a lone electron pair.^{57,198–200,231} These substances may come from medications, food, or be synthesized in the body.²³² The influence of such substances may reduce therapeutic effects, as well as associated side effects.²³³ Understanding these interactions, that is which substances and to what extent bind with Platinum drugs, can help adjust medical doses to maintain their optimal effect.

The use of nanostructures in the anticancer treatment of lung cancers seems to be a good solution. For example, the creation of nanomedicine should reduce the high toxicity of Platinum-derivative compounds by not only repeatedly reducing the doses of the chemotherapy drug, but also by directing the drug directly to the cancer site, while bypassing healthy human cells. Moreover, nanomedicine solves the problem of the chemotherapy drug binding to amino acids during distribution in the peripheral blood and binding to other structures similar to nitrogenous bases at the cellular level.

Nanostructures

When Richard Feynman introduced the concept of nanotechnology in 1959,^{234–238} he did not think it would be one of the most promising technologies in medicine of the twenty-first century. Using nanotechnology improves diagnosis, treatment, and prevention and enables people to understand the human body.^{239–253} Nanostructures can also lead to the improvement of drugs. Application of nanostructures can remove the disadvantages of drugs and simultaneously highlight their advantages. To reduce the side effects of some drugs and increase the effectiveness of the treatment, nanostructures have been used for drug delivery. Because nanostructures are molecules whose external dimensions are in the range of 1 nm–100 nm^{151,254–256} (see Figure 8), they have a much larger surface area than their volume, which makes them perfect drug carriers.

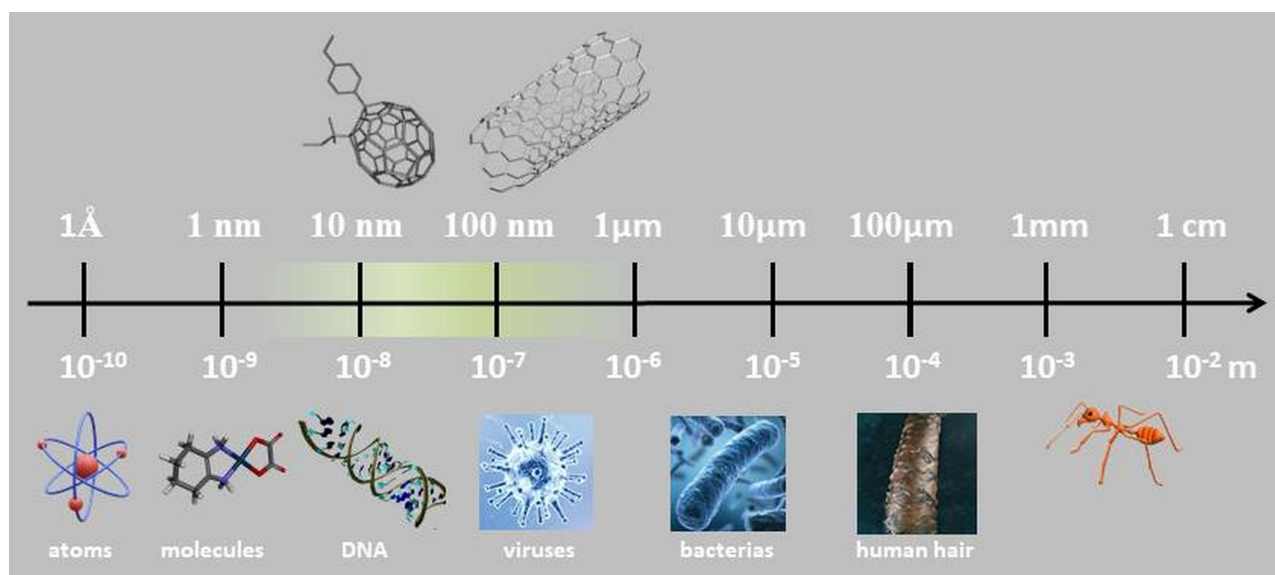


Figure 8 The 1 Å – 1 cm scale. The scale provides the size of exemplary objects, corresponding to a given dimension on the scale.^{151,254–256}

This allows the dosage of the drug to be limited to an absolute minimum, and thus reduces the toxic effect.²⁴⁹ The insides of nanostructures, eg empty fullerene cages, can also protect drug molecules from inactivation before reaching the target site. As we know, Platinum-derived compounds have low selectivity and react with many different compounds, structurally similar to purines containing an aromatic ring with lone pairs of electrons on the N7 atom.^{57,102,198–200} One of such groups are B vitamins, which are supplied, for example, with food.^{57,102,198–200}

General Division of Nanostructures

Nanostructures are a wide range of different systems which, due to various criteria, can be divided into many classes.^{257–276}

The first criterion is the number of dimensions at the nanoscale. If there is only one dimension, such nanostructures are called nanoplates.²⁷⁷ Whereas, when two of the three dimensions are present at the nanoscale, these structures are called nanofibers.²⁷⁸ When all dimensions are at the nanoscale, we talk about nanoparticles (liposomes, quantum dots, and fullerenes).^{151,254,277,279,280}

Secondly, the classification can be based on their chemical composition and include organic, inorganic, and carbon-based nanostructures, as shown in Figure 9.

The third way of classifying nanostructures is the criterion of drug delivery technology, which includes biologic, polymeric, carbon-based, and metallic-based systems,²⁸⁶ as described in Table 4.

Fate, Side Effects and Biodegradability of Nano Systems in vivo

Nanostructures with Platinum-derivative drugs are administered intravenously, increasing the accumulation of structures at the target site using targeting, which can be divided into active and passive.²⁸⁷ Passive targeting involves adding drugs to a specific area of nanostructures so that the drugs gain new pharmaceutical and physicochemical properties that result in increased accumulation at the tumor site.^{288,289} Active targeting, on the other hand, involves adding a nanostructure that is specifically targeted to a particular receptor or a biomarker located on target-specific cells on which drugs are to act. After reaching the target site, the drug is released, but the fate of the nanostructure does not end in this place. They have two most popular routes: intracellular degradation in endosomes and lysosomes, or they remain in the bloodstream and undergo opsonization and clearance in the process of phagocytosis.²⁹⁰ Phagocytosis most commonly takes place in the liver and spleen by macrophages, depending on individual properties such as surface properties or size.^{291,292} However, removal from the lungs takes place chemically and physically, eg in the area of the alveoli, absorbed by macrophages.²⁹³

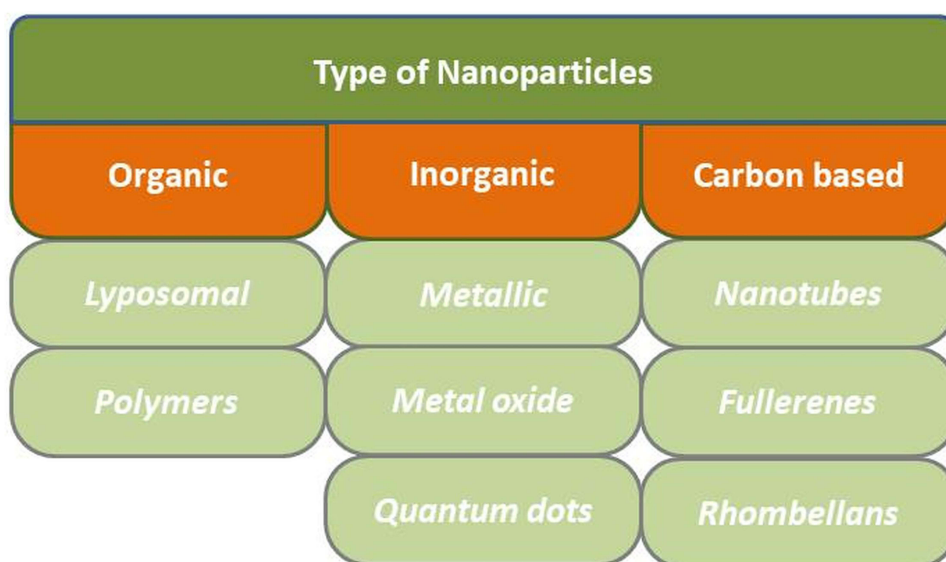


Figure 9 Division of nanoparticles.^{249,278,281–285}

Table 4 Nanostructure Classification by Drug Delivery Technology.²⁸⁶

Biologic:	<ul style="list-style-type: none"> • Liposomal • Protein Nanotubes • Exosomes • Viruses • Nanobodies
Polymeric:	<ul style="list-style-type: none"> • Hydrophilic Polymeric • Micelles • Dendrimers • Hydrogels • Nanoemulsions • Quantum Dots
Carbon-based:	<ul style="list-style-type: none"> • Nanotubes • Fullerenes • Rhombellans
Metallic-based:	<ul style="list-style-type: none"> • Gold • Silver • Palladium • Magnetic nanostructures

The following side effects can be generated by nanoparticles:

- oxidative stress, which can cause inflammation, then genotoxicity, and finally apoptosis,
- genotoxicity, which may be limited to DNA strand breaks, chromosome fragmentation, the formation of oxidative adducts, and, consequently, changes in gene expression,
- enhancing cytokine production,
- damage to lysosomes and mitochondria,
- autophagy dysfunction.²⁹⁴

These effects depend on the properties (eg carbon nanotubes have negligible toxicity) and concentrations of specific compounds (eg lipid nanoparticles are toxic at a concentration of 500 µg/mL and nontoxic below 200 µg/mL).^{295,296}

Nanomaterials as Carriers for Drugs in the Treatment of Lung Cancer

The use of nanocarriers in the treatment of lung cancer requires them to overcome the physiological and anatomical protective barrier of the lungs. Nanotechnology has changed the way in which nanocarriers are used in the treatment of lung cancer, which offers enormous opportunities for the future.²⁸⁹ Physicochemical properties such as size, shape, stiffness or surface properties are extremely important in determining the distribution capabilities of nanoparticles.²⁹⁷ Due to the fact that tumor blood vessels have a diameter of approximately 100–600 nm,^{190,194,298–305} nanoparticles with a size of 10–100 nm and a molecular weight above 50 kDa are ideal nanoparticle for drug delivery systems.²⁸⁹ Moreover, nanoparticles smaller than 150 nm can avoid uptake by macrophages in the RES.³⁰⁶ Because nanoparticles are larger than 10 nm, they can also avoid capillary leakage.³⁰⁷

A general distinction is made between organic and non-organic nanoparticles (NPs) in the treatment of lung cancer.²⁸⁹ In the first (organic) group, one can include:

- solid lipid NPs
- liposome-cholesterol and phospholipid-like biofilm-like NPs,
- nanostructured lipid carriers-NPs mixed with solid lipids and liquid lipids,

- polymeric micelles-colloidal NPs composed of amphiphilic block copolymers,
- polymeric NPs composed of polymers such as sodium alginate, chitosan, gelatin, polycaprolactone, polylactide, and polylactic acid,
- dendrimer-highly branched, symmetrical, radiating NPs.

The second one (non-organic) encompasses:

- carbon nanotubes-hydrophobic tubular structures made by carbon atoms with diameters between 4 nm and 100 nm,
- magnetic NPs-superparamagnetic materials with a size > 25 nm,
- quantum dots-colloidal NPs with atomic properties.³⁰⁸

There are many examples of clinically used nano- drugs in the treatment of lung cancer in the literature. These examples are presented in [Tables 5 and 6](#). In the [Table 5](#) nanomedicines contain Pt drugs, while nano-drugs built from other compounds than Platinum are presented in [Table 6](#).

Nanoparticles can have passive or active anti-cancer properties. Among the first, there are three techniques, but only two of them have been used in anti-cancer treatment in the human body. In the first case, the acidic microenvironment of tumors is used to limit the action of NPs to acidic conditions.²⁸⁹ In the second one, because NPs are positively charged, the tumor cells can be used to carry additional negative charges.³¹³ Active targeting gives the effect of precise targeting by placing ligands on the surface of the nanoparticle, thanks to which it is possible to attach, for example, enzymes that recognize receptors in the blood vessels of the tumor.^{265,270,314,315} Bazak et al.,³¹⁶ showed that in some cases, receptors and ligands help inhibit tumor drug resistance by facilitating endocytosis. Various types of ligands can be found in the literature, such as polymers,^{265,270,314,315} small molecules, fragments, antibodies and aptamers (APTs).^{311,317–319} In the treatment of lung cancer, numerous receptors have been used that have the ability to increase the specific binding of a nanoparticle containing a drug ([Figure 10](#)).³²⁰

Table 5 Nanodrugs Used in Lung Cancer Containing Platinum Compounds^{309,310,316}

Trade name	Components	Types of tumors	Clinical trial status	Administration route
Lipoplatin	Liposomal Cisplatin	NSCLC	In clinical Phase III	Intravenous infusion
SPI-77	Liposomal Cisplatin	NSCLC	In clinical phase II	Intravenous infusion
Aroplatin	Liposomal cis-bis-neodecanoato-trans-R,R-1,2- diaminocyclohexane platinum (II)	Malignant Pleural Mesothelioma	In clinical phase II	Intravenous infusion
RT-LC03	Nanobody Envafohimab Cisplatin	NSCLC and SCLC	In clinical phase II	Intravenous infusion
AP5280	HPMA Polymer Cisplatin	Solid Tumors	In clinical phase I	Intravenous infusion
ProLindac or AP5346	Hydrophilic Polymer DACH-Pt	Solid Tumors	In clinical phase I	Intravenous infusion
Platinum PAMAM complex	PAMAM (poly(amidoamine)) Dendrimer Cisplatin	NSCLC	In vitro study	Intravenous infusion
Poly(l-glutamic acid)-cisplatin	Micelle PEG-b-poly (glutamic acid) Cisplatin	NSCLC	In clinical phase II	Intravenous infusion

Table 6 Nanodrugs Used in Lung Cancer Containing Other Than Platinum Compounds.³¹²

Trade name	Components	Types of tumors	Clinical trial status	Administration route
Doxil or Caelyx	PEGylated Liposomal Doxorubicin	NSCLC	FDA Approval 1995	Intravenous infusion
L-BLP25	BLP25 LiposomeVaccine	NSCLC	In clinical phase II	Subcutaneous infusion
LEP-ETU	Liposomal Paclitaxel	Lung Cancer	In clinical phase I/II	Intravenous infusion
LIPUSU	Paclitaxel Liposome and Cisplatin	Squamous NSCLC	In clinical Phase IV	Intravenous infusion
LY01610	Hydrochloride Liposome Irinotecan	Extensive-stage SCLC	In clinical phase II	Intravenous infusion
ONIVYDE	Liposome Irinotecan	SCLC	In clinical phase III	Intravenous infusion
OSI-211	Liposomal Lurtotecan	SCLC	In clinical phase II	Intravenous infusion
Genexol-PM	Polymeric Micelle Paclitaxel	NSCLC	Approval in Europe 2013, Korea 2007	Intravenous infusion
PM-03-2015	Paclitaxel Micelles and Cisplatin	NSCLC	In clinical phase III	Intravenous infusion
Combixen	Iron oxide nanoparticles	SCLC	NDA field	Intravenous infusion
CYT-6091	TNF- α bound PEGylated colloidal Gold particle	Solid tumor	In clinical phase I	Intravenous infusion
Photofrin	Porfimer sodium	NSCLC	FDA Approval 1995	Intravenous infusion
ABI-007	Nanoparticle albumin Paclitaxel	Advanced NSCLC	In clinical phase II	Intravenous infusion
ABI-009	Protein-bound nanoparticles Rapamycin	Neuroendocrine Tumors	In clinical phase II	Intravenous infusion
Nab-paclitaxel	Nanoparticle albumin Paclitaxel	Advanced or metastatic squamous lung cancer.	In clinical phase II	Intravenous infusion
DOTAP:Chol-TUSC2 or FUS1	TUSC2-nanoparticles Erlotinib	NSCLC	In clinical phase II	Intravenous infusion
BIND-014	Polymeric nanoparticle Docetaxel	NSCLC	In clinical phase II	Intravenous infusion
ONC-003	Quaratusugene Ozeplasmid Osimertinib	NSCLC	In clinical phase II	Intravenous infusion
CRLX101	Cyclodextrin-polyethylene glycol Camptothecin	NSCLC	In clinical phase II	Intravenous infusion
EP0057	Cyclodextrin-polyethylene glycol Camptothecin	SCLC	In clinical phase II	Intravenous infusion

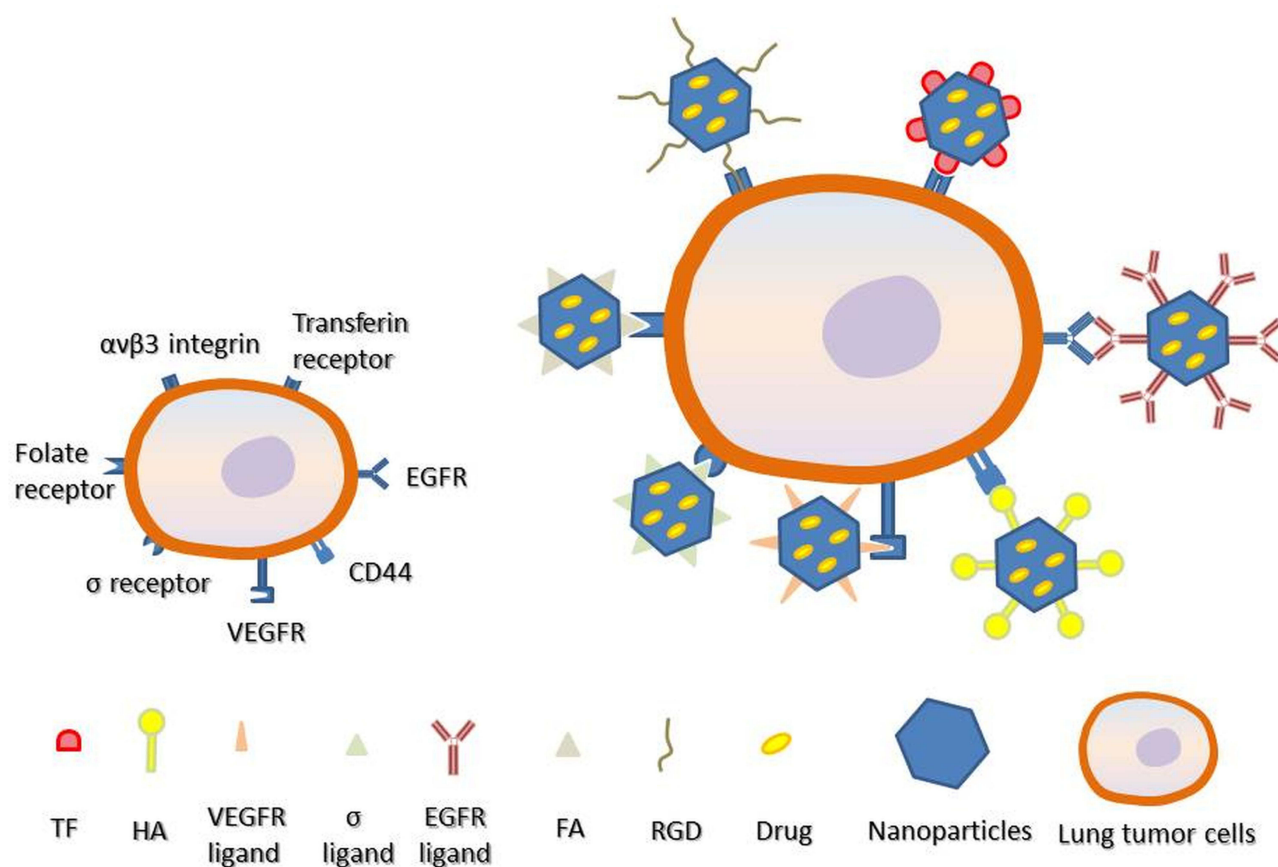


Figure 10 Lung cancer with cell receptors used as targets (right side of the Figure) and the nanoparticles with anticancer drugs and with a specific ligands structure (left side of the Figure and bottom of the drawing) used in targeted anticancer therapy.^{288,289,321}

- **Epidermal Growth Factor Receptor (EGFR)** due to its structure³²² plays a crucial role in the advancement of carcinoma. There is an external and internal fragment of tyrosine kinase activity. An extracellular section includes the ligand-binding area responsible for the regulation of tumor growth (invasion, angiogenesis, metastasis, and proliferation of cells). The binding of the ligand to the attachment region causes conformational modifications. Further, the binding of ligands and the activity of tyrosine kinase lead to autophosphorylation that triggers alterations in the signaling.^{323–328}
- **Growth Hormone Receptor (GHR)** is a single-pass transmembrane receptor with at least one cytokine receptor homology domain (CRHD) in its extracellular portion. The CRHD has two fibronectin III (FNIII)-like folds. GHR overexpression has been identified in A549 NSCLC and other related cancers.^{288,329,330}
- **Folate acid (FA) Receptor**, the folate receptors demonstrate a greater binding affinity for folic acid, which is composed of four forms of the receptor: Folate Receptor Alpha (FRA), Folate Receptor Beta (FRB), Folate Receptor Gamma (FRG) and Folate Receptor Delta (FRD). Folate Receptor Alpha (FRA) glycosylphosphatidylinositol-anchored glycoprotein placed on the cell surface, referred to as FOLR-1 or folate binding protein (FBP), assists in the delivery of 5-methyltetrahydrofolate (5-MTF). Overexpression of the FRA has been observed in lung-like solid tumor types, but several studies have reported elevated levels of overexpressed FRA in NSCLC.^{288,331–340}
- **Vascular Endothelial Growth Factor Receptors (VEGFR)**, vascular permeability factor, lead to vascular leakage. There are three major types of tyrosine kinase receptors, namely FLT-1 (VEGFR1), FLK-1 (VEGFR2), and FLT-4 (VEGFR3), which show the ability to bind only with mammalian VEGFR. These receptors are frequently

overexpressed in NSCLC and possess an acknowledged significance in the angiogenesis, proliferation, and metastasis of tumor cells.^{341–345}

- **Fibroblast Growth Factor Receptor (FGFR)**, the extracellular component, made up of immunoglobulin resembling domains with affinity for the FGF ligand, consists of a transmembrane region, and possesses tyrosine kinase activity. Unusual signaling of FGF/FGFR, amplification or alterations of genes (oncogenic) may contribute to tumorigenesis and therapy resistance in various cancers such as solid tumors and malignant melanoma. Elevated expression of FGFR1 is reported in NSCLC with varying ratios in squamous cell carcinomas and lung adenocarcinomas.^{346–350}
- **σ receptor**, membrane-bound protein sigma receptors, σ_1 (sigma-1) and σ_2 (sigma-2). Overexpression of σ_2 receptors showed six out of 15 human adenocarcinoma samples and twelve out of 15 human SCLC samples.^{351–362}
- **Human transferrin (TF) Receptor**, an iron-binding protein to transfer iron absorbed via the digestive tract and iron released by red blood cell degradation into bone marrow in the form of the TFR-Fe³⁺ complex to generate mature red blood cells and transporting iron into cells that express TFRs.³⁶³ TFR is expressed at a modest level in all normal nucleated cells. The ligature shows that expression level is higher in cells with a high proliferation rate, especially in tumor cells, such as chronic lymphocytic leukemia, liver cancer and lung cancer.^{364–371} Also, low molar concentration of artemisinin after pretreatment could kill the cells in SCLC. Thymoquinone-NP modified transferrin enhances the apoptosis and death cascade of NSCLC cells, and limits these migration cells without a toxicity effect.³⁷²
- **$\alpha v \beta 3$ Integrin**, consists of non-covalently linked alpha and beta subunits and belong to the transmembrane heterodimeric glycoprotein family. There are 24 distinct integrin receptors, which depending on the orientation patterns, exhibit between of 18 α and 8 β subunits. Integrins are detected in almost 82% of all NSCLC patients, regardless of differentiation type or degree. However, 13% of SCLCs demonstrated an overexpressed $\alpha 3 \beta 1$. Downregulated levels of integrin expression have been related to SCLC, as well as the disease's high severity and potential to spread.^{289,373–375}
- **CD44**, membrane-bound glycoprotein, plays an important role in malignant tumor-related activities used as a cancer stem cell (CSC)/tumor-initiating cells (TIC) marker.³⁷⁶ CD44 has overexpressed in solid tumors, such as pancreatic cancer, breast cancer, and lung cancer.^{377–379} The receptor is involved in many signal cascades that mediate tumor enhancement and can indirectly activate cell proliferation pathways through ligands and activate anti-apoptotic pathways.³⁸⁰ In the case of SCLC, activation of CD44-MAPK-PI3K signal transduction results in increased invasiveness and multi-drug resistance phenotype of lung cancer cells.

A factor promoting the use of receptors in combination with a nanostructure in the treatment of lung cancer is the fact that the receptors themselves are significantly overexpressed only in cancer cells.³⁸¹ Therefore, their use brings benefits in the form of reducing side effects and improving the effectiveness of treatment. For example, the σ receptor induces³²⁰ cell death only in cancer tissue, but never in unaffected (stem) cells. However, TFR, while showing high expression, also shows high histological specificity. Its expression in lung adenocarcinoma is much higher than in other histological types.²⁸⁹ Since TF plays an important role in the abnormal iron metabolism of lung cancer cells, the iron uptake by lung cancer cells can be inhibited through this receptor, which will ultimately affect the proliferation of pathological cells. It has also been shown that FR activity is higher in diseased cells compared to physiological cells.²⁸⁹

In the case of nanomedicine treatment, the route of administration may be different, not only through injections into the peripheral blood. A new direction in the development of nanostructures for the treatment of lung cancer is the use of drug delivery by inhalation. This allows to reduce the dose of the drug without weakening the effect because the local concentration will be appropriate, and moreover, such a kind of application could limit the absorption into the bloodstream and thus reduce the side effects.³⁷⁴ The nanostructures used for inhalation are polymers and lipids, which increase bioavailability, stability and stay longer at the target site. The key requirements for a nanostructure to be used in inhalants are its size, from 10 to 100 nm, based on an animal model, and its surface-active properties, which are intended to prevent phagocytosis by macrophages.³⁸² Animal studies have confirmed that in the case of inhalation, the accumulation

of drugs in target sites is higher than when using the intravenous route.^{383,384} What is more, such application reduces concentrations in the liver, spleen and kidneys compared to intravenous administration.³⁸⁵

Examples of Applications of Nanostructures with Platinum Compounds

There are many examples of nanostructures combined with Platinum drugs in the literature. Platinum compounds, due to their low selectivity and increased resistance, are often combined with nanostructures. In the area of organic nanostructures, the following combinations with Platinum-derived drugs can be distinguished:

- protein nanotubes,³⁸⁶
- liposomes,^{85,387–400}
- nanobodies,⁴⁰¹
- polymers,^{402,403}

while inorganic nanostructures are represented by

- dendrimers,^{403–405}

and among the representatives of the carbon-based ones, there are

- nanotubes,^{406–418}
- rhombellans.^{260,419–421}

The wide variety of nanostructures means that Platinum-based drugs can be located both on the surface of nanostructures, eg fullerenes and nanotubes, and inside, eg liposomes and nanotubes. These structures can, like liposomes, fuse with the cell membrane and release chemotherapeutics directly into the cell, or they can disintegrate in the acidic environment located near the tumor and be released there (polymer ProLindac^{403,422}). Among the nanostructures transporting Platinum, both active (antibodies) and passive (nanotube (cis,cis,trans-Pt(NH₃)₂C₁₂(OEt)(O₂CCH₂CH₂CO₂H) and SWNCT^{406,407}) targeting can be found.

This diversity makes it difficult to describe in detail all nanostructures combined with Platinum-derived drugs, apart from the general facts that nanostructures increase stability, protect Platinum-derived drugs against inactivation in the blood, increase accumulation in cancer tissues, and reduce side effects, while increasing selectivity.

These combinations are widely described in the literature, and in situ, in vitro, and in vivo studies, as well as clinical trials are very promising. Unfortunately, they have not yet been introduced to the market, but when they are, they will probably significantly improve the survival rate and quality of life of patients.

Protein Nanotubes

Protein nanotubes are nanotubes made of peptide and/or protein fragments that have been connected, for example, by self-assembly or by creating a pulsed electric field. Compared to classic nanotubes, they are more biocompatible and biodegradable. Moreover, they can undergo surface and internal modifications, enabling the effective and controlled release of substances.⁴²³ According to in vivo mouse studies, protein nanotubes from the plant virus TMV (tobacco mosaic virus) in combination with Cisplatin are an effective method in the treatment of ovarian cancer. The nanostructure consists of TMV monomers, in which each monomer is composed of 2130 identical copies of a coat protein, and each coat protein has two glutamic acids. TMVs were taken from *Nicotiana benthamiana* plants, multiplied, and formed into 300×18 nm nanotubes that can accommodate cisplatin molecules in a 4 nm wide empty channel. What is important to emphasize is that TMV is safe for humans because it does not infect mammals. The results of the study prove that highly distributed TMV-cisPt showed better effectiveness and accumulation within tumors than free Cisplatin.³⁸⁶ The plant virus TMV in combination with Cisplatin was tested in mice using Alanine Transaminase (ALT), Aspartate Aminotransferase (AST) (both are indicators of liver injury), and Kidney Injury Molecule 1 (KIM-1) assays. Mice were administered

solutions containing Cisplatin alone, TMV- cisPt, TMV in Phosphate Buffered Saline (PBS) and a control containing only PBS in three injections on days 7, 10 and 14, and toxicity was examined on days 15 and 19 after tumor implantation. As shown by the results of the ALT test, all results were within the norm, unlike the AST tests, where on day 15, the TMV- cisPt, indicated potential hepatotoxicity, but on day 19, the results were normal. On the other hand, no renal toxicity was reported.³⁸⁶

Liposomes

Liposomes are bilayer delivery vehicles made of phospholipids and an aqueous core^{84,388,394–396} (Figure 11).

These nanostructures have a wide spectrum of use, because they can be applied to both hydrophilic and hydrophobic drugs. Liposomal delivery of small-molecule drugs has presented many advantages, such as the highest local drug concentration, reduced toxicity, and better LADME (liberation, absorption, distribution, metabolism, and excretion). Natural phospholipids possess low toxicity and weak immunogenicity. Disadvantages include rapid circulation clearance, a low half-life time, and worse penetration of such structures.

Currently, in clinical trials, there is Lipoplatin (9% Cisplatin and 91% lipid), the phospholipids' bilayer of which contains dipalmitoylphosphatidylglycerol, soy phosphatidylcholine-3, and DSPE-PEG 2000 cholesterol. However, Lipoplatin, instead of using copper receptors, delivers cisplatin by fusion with the cell membrane and releases cisplatin into the cell, which avoids membrane resistance. Inside the cell, Cisplatin activates mitochondria and other pathways leading to apoptosis. In preclinical studies on rodents, this combination had lower toxicity than normal Cisplatin. The main side effects reported were neutropenia and gastrointestinal toxicity, but unlike Cisplatin, hepatotoxicity, neuropathy, cardiotoxicity, ototoxicity, and hair loss were not reported. The use of Liposomal deserves special mention because of its significantly reduced nephrotoxicity, which is a major Cisplatin dose limit marker. Furthermore, compared with normal tissues, it was much higher than Cisplatin. The accumulation of lipoplatin in cancerous tissues was higher than in healthy tissues, up to 221 times higher for colon tumors; additionally, Lipoplatin reacted more often, causing cell damage 10 to 171 times more often in cancer cells than in healthy cells. Prospectively, it may significantly reduce side effects by

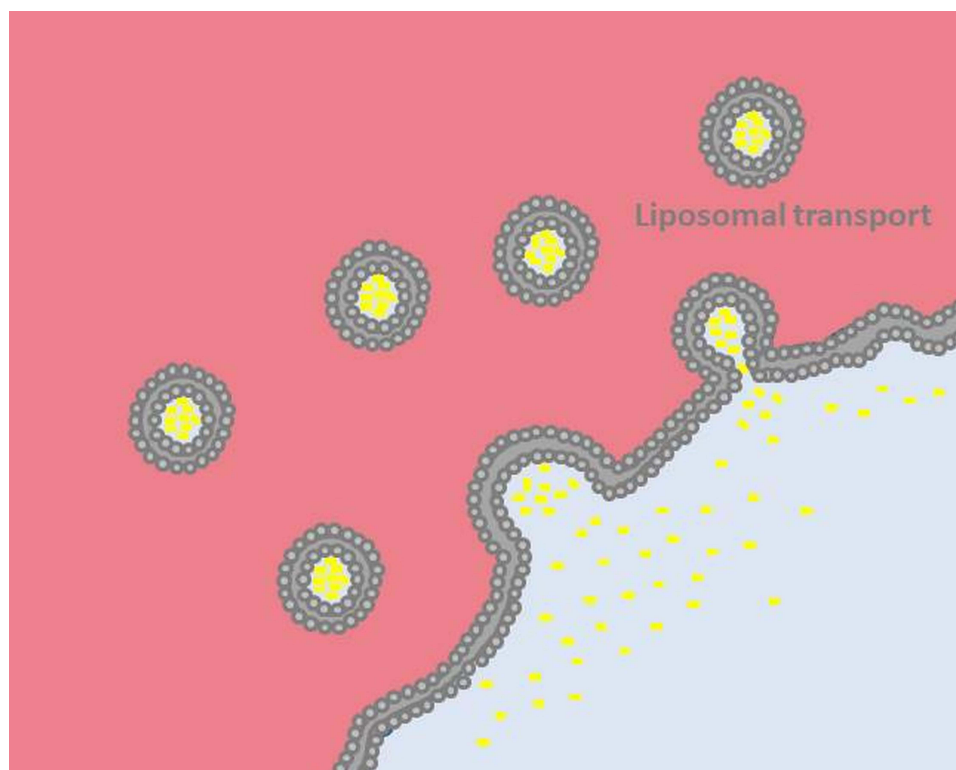


Figure 11 The scheme of liposomes.³⁹⁴

improving selectivity. In the second phase of trials, Lipoplatin was combined with gemcitabine and used in the treatment of patients who were resistant to Platinum chemotherapy. The European Medicines Agency gave Lipoplatin an orphan drug status for treatment of pancreatic adenocarcinoma^{275,279–282,284,285,312,313}.

Another liposomal drug with Cisplatin is SPI-77 (cisplatin: lipids ratio is circa 1:70), the bilayer of which consists of hydrogenated soy phosphatidylcholine, cholesterol, and DSPE-PEG200. The results of the first phase of clinical trials showed much fewer side effects compared with Cisplatin. Despite the fact that accumulation in tumor tissues was four times greater, antitumor activity was the same or less.^{388,398}

The pH-sensitive liposomal formulation for Cisplatin is SpHL-CDDP, which consists of dioleoylphosphatidylethanolamine, unsaturated phosphatidylethanolamine, cholesteryl hemisuccinate, and DSPE-PEG 2000. Unsaturated phosphatidylethanolamine improves the release into the cell, whereas cholesteryl hemisuccinate gives properties of rapid release at acidic pH because, when the pH reaches acid values, it induces a destabilization formulation and releases Cisplatin. The survival rate in the ascitic tumor was much higher after using SpHL-CDDP than Cisplatin.^{389,395}

The first combination of liposomes with Oxaliplatin is Aroplatin (drug: lipids ratio is 1:15), which consists of dimyristoylphosphatidylcholine and dimyristoyl phosphatidylglycerol. In the second clinical study, the response was good, though there was a problem with drug distribution and some tissues were not exposed to the Aroplatin.³⁹⁰

The next combination of Oxaliplatin is Lipoxal, which in the first clinical study phase had high effectiveness for gastrointestinal cancer and lower toxicity compared with Oxaliplatin.⁸⁴

Nanobodies

In 1993, a heavy-chain antibody was discovered which, unlike regular antibodies, was naturally deficient in light chains.⁴²⁴ The structure of a heavy chain antibody includes two constant regions, ie a hinge region and a heavy chain variable domain, which, when isolated, give us nanobodies. Nanobodies are artificially obtained single-domain antibody molecules. They have an oval shape with dimensions of 4 nm × 2.5 nm × 3 nm and a molecular weight of 12–14 kDa (compared to ordinary antibodies (150 kDa) is approximately 1/10 of the molecular weight of conventional antibodies).

Compared to regular antibodies, a nanobody is characterized by lower immunogenicity, better tissue penetration, and higher stability. However, they have a shorter half-life. From a manufacturing standpoint, they are easier to modify and cheaper to produce. They also demonstrate high targeting ability.

Types of nanobodies include monovalent nanobodies, bivalent nanobodies, bispecific nanobodies, multivalent nanobodies, and nanobodies fused with other fragments, for instance Platinum drugs (Figure 12). Most nanobodies are currently in the clinical phase, but nanobodies are starting to enter the market and are used, for example, in the treatment

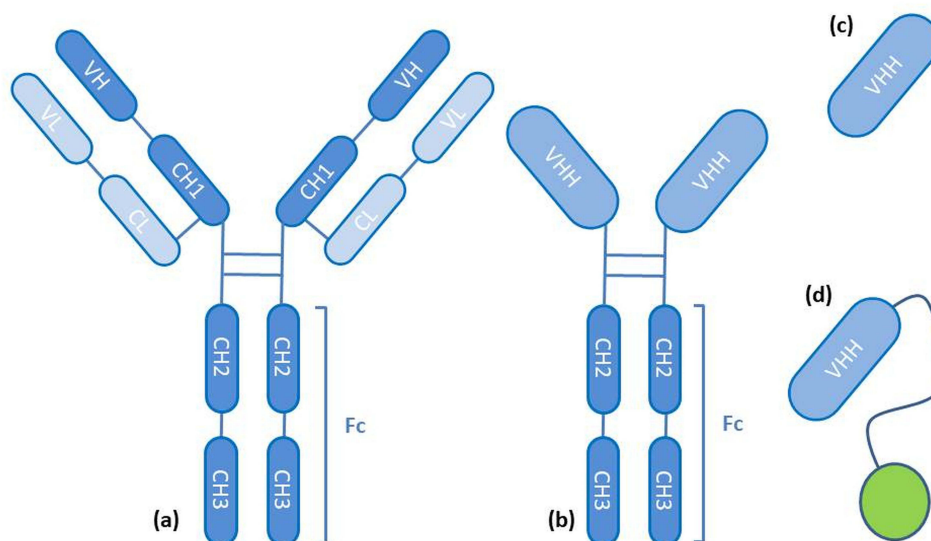


Figure 12 The scheme of (a) conventional, (b) heavy-chain antibodies, regular antibodies (c) and nanobodies fused with other fragments (d).⁴²⁴

of thrombotic thrombocytopenic purpura and multiple myeloma. Envafohimab is used in solid cancers, including non-small cell lung cancer, because, like Durvalumab and Atezolizumab ([Supplementary Materials, Table S1-S2](#)), it targets the protein programmed cell death-ligand 1 (PD-L1).^{425–429} An example of a combination of a nanobody with a Platinum drug is the combination of a biparatopic anti-EGFR nanobody (N, 7D12-9G8) synthesized by oxidizing cisplatin (maleimide-functionalized Pt(IV) prodrug [Pt(NH₃)₂Cl₂(OH)(OAc)]). The drug accumulation is clearly higher in the EGFR-positive A431 cells than in the EGFR-negative A375 cells. Cisplatin showed strong toxicity, in contrast to the nanobodies themselves, which showed very low cytotoxicity; the survival of EGFR-positive cells was approximately 75%, and for EGFR-negative cells, it was over 90%. In the case of combining a nanobody with a Platinum-derivative drug, the cytotoxicity to EGFR-positive cells was high - survival rate was only 15%, while the cytotoxicity to EGFR-negative cells was very low and similar to the cytotoxicity of nanobodies alone (survival rate of over 90%), which proves that the drug conjugate nanobody with Platinum has much lower systemic toxicity than cisplatin. Moreover, nanobody conjugation improves pharmacokinetics and increases drug retention, which leads to an increased therapeutic effect.⁴⁰¹

Polymers

The third group of nanostructures connected with Platinum drugs are hydrophilic polymers. The most common polymer for anticancer drugs is N-methacrylamide (HPMA), which enhances therapeutic efficacy and decreases side effects. Furthermore, the connection of drugs with HPMA increases accumulation in tumor tissues.²³⁴

AP5280 is a combination of Cisplatin and HPMA (mass ratio 1:10). These results of these *in vivo* studies show a 19-fold higher accumulation in tumors and a 20-fold lower toxicity, as well as promising efficacy.⁴³⁰

ProLindac (AP5346) contains dichloro(1,2-diaminocyclohexane)Platinum(II) (DACH-Pt) and a hydrophilic polymer. This combination is stable at physiological pH and remains inactive, but at acidic pH, which is nearby the tumor surroundings (presumably the tumor extracellular fluid or the interior of the tumor cell), releases the Platinum drug. ProLindac presented a 16-fold better delivery to the tumor and, what is worth highlighting, a 14-fold one to tumor DNA. For this reason, the anticancer activity of this combination is much better, and the side effects are much lower in comparison with Cisplatin.⁴²⁹ In the first phase of clinical trials, dose-limiting neutropenia occurred only at the highest dose, and the main side effects included typical nausea and vomiting, and renal toxicity. However, these effects can be prevented by properly preparing the patient for chemotherapy by giving him appropriate antiemetics and hydrating him. These results correspond to the results of Phase 2 clinical trials and correspond to the frequency and severity of expected side effects of Platinum-based drugs.⁴³¹

An innovative method is to combine Cisplatin with PLGA-block-polyethylene glycol and with the epidermal growth factor receptor. This method turned out to be effective in triple-negative breast cancer. Using epidermal growth factor receptors improves selectivity and therapeutic efficacy compared to untargeted and free Platinum drugs.⁴³

AP5280 consists of a cytotoxic Pt complex combined with a water-soluble, biocompatible, non-toxic polymer backbone consisting of poly-N-(2-hydroxypropyl)methacrylamide. The platinum content by weight is approximately 8.5%. As indicated by Phase I studies, the use of nanostructure extends the residence time in the bloodstream and reduces renal toxicity and myelosuppression.⁴³⁰

Dendrimers

Another type of nanostructures are dendrimers. They contain in their center a small molecule or a polymer core, from which numerous side chains branch off, which sequentially branch again ([Figure 13](#)). Multiple end groups allow the conjugation of various molecules in the core or at the surface, for instance, Platinum drugs. Drugs connected with these structures are characterized by lengthened half-life, higher stability, selectivity, water solubility, tumor accumulation, as well as decreased immunogenicity, antigenicity, and toxicity.^{404,405,432} The preclinical research on complexes of Cisplatin and Dendrimers began as early as 1999.^{431,432}

The complex of Cisplatin and poly(amidoamine) dendrimer containing a carboxylate surface group acted against cisplatin-resistant (squamous) cancer, causing a decrease in toxicity and an increase in accumulation in tumor tissues through increased permeability and retention effect.^{404,405,435,436}

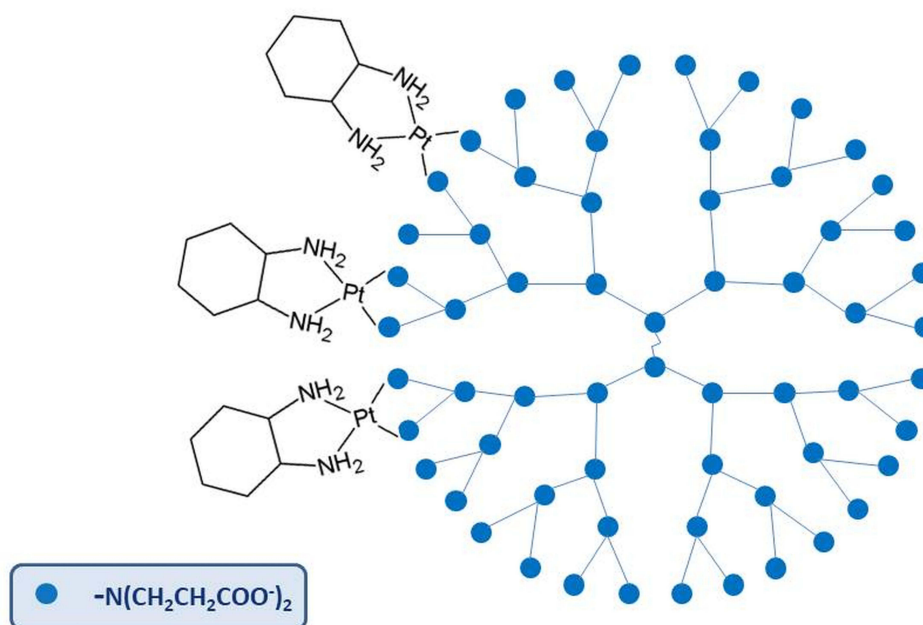


Figure 13 Structure of a dendrimer.^{404,405,432–436}

Carbon Nanotubes

Carbon Nanotubes (CNTs) were discovered by a Japanese physicist Sumio Iijima in 1991.⁴³⁷ They are universal nanostructures with a wide range of applications resulting from unique properties, such as high resistance to stretching, high conductivity of heat and electricity, low weight, low toxicity, and a high aspect ratio, which increases the ability to penetrate into the cell. In fact, it is assumed that nanotubes pierce the cell membrane like needles. In addition, CNTs enter the cell through the membrane via endocytic pathways. Furthermore, they are characterized by greater accumulation in cancerous tissues than in normal tissues.^{25,34,116,117,161,162,395,438,439}

Due to their structure and huge surface area, they have excellent abilities as drug transporters. This means that the drug can be placed outside the nanostructure using covalent and non-covalent bonds, as well as inside, where it does not require the modification of its structure by adding further bonds. The center has a higher and favorable binding energy in the direction of absorption, which means that the CNT-drug bonds are not needed. Importantly, hiding the drug inside protects it to a greater extent against interactions with external substances, other drugs, deactivating agents, or the unfavorable influence of the environment itself. Due to the type of structure, we divide them into single-walled (SWCNT) and multi-walled nanotubes (MWCNT).^{440,441}

Various combinations of Platinum compounds and nanotubes can be found in the literature. Firstly, an *in vitro* study was presented in which Platinum(IV) complex *cis,cis,trans*-Pt(NH₃)₂Cl₂(OEt)(O₂CCH₂CH₂CO₂H)] and SWCNT have been non-covalently functionalized with an amine-ended PL-PEG chain (Figure 14).

As indicated by studies, this complex enters the cell by clathrin-dependent endocytosis and, thanks to the reducing environment of endosomes, releases Platinum compounds inside the cell. Drug release at low pH is facilitated by the loss of the axial properties of the ligand by which it is linked to SWCNT. This is an extremely important property, considering that many cancer tumors have a low pH. As research confirms, the addition of a nanotube increased the concentration in cancer cells 6–8 times compared to the free complex, and was 2 times higher than the Cisplatin used. This proves the effectiveness of using SWCNTs as transporters for Platinum compounds.⁴⁰⁶ The second *in vitro* study is a modification and extension of the tumor cells that highly overexpress the folate receptor (Figure 15). In the studies, these complexes were 8.6 times more effective against cancer cells than Cisplatin.⁴⁰⁷

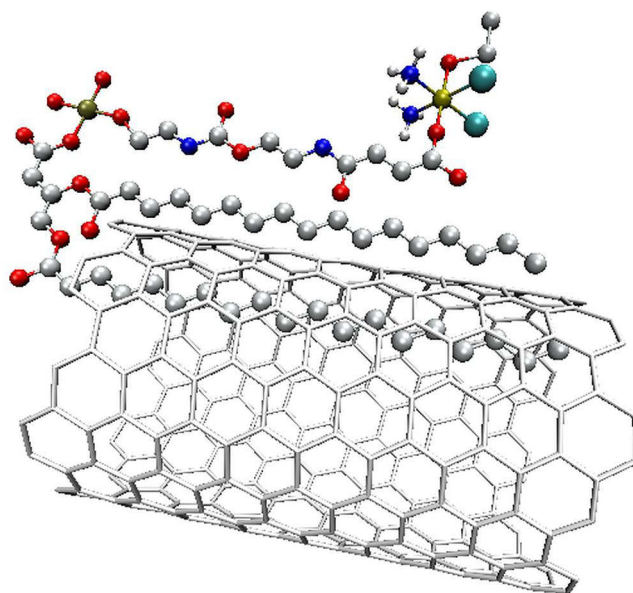


Figure 14 The structure of Platinum(IV) complex $\text{cis,cis,trans-Pt}(\text{NH}_3)_2\text{Cl}_2(\text{OEt})(\text{O}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H})$ with SWCNT, functionalized with PL-PEG.⁴³⁸

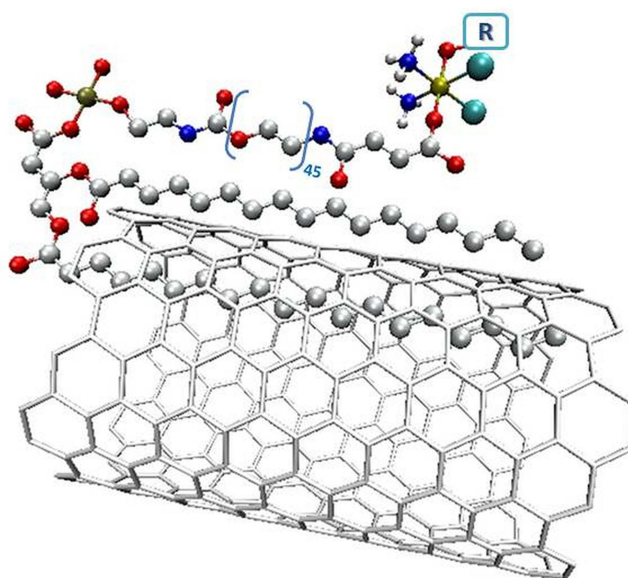


Figure 15 The structure being a modification and extension of the Platinum(IV) complex $\text{cis,cis,trans-Pt}(\text{NH}_3)_2\text{Cl}_2(\text{OEt})(\text{O}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H})$ with SWCNT, functionalized with PL-PEG, in which additional molecules were added to the complex.⁴⁴² Symbol R means the targeted molecule containing folic acid (vitamin B9) with the structural formula $(\text{O}_2\text{CCH}_2\text{CH}_2\text{CONH-PEG-FA})$.

Another study describes a complex hydrophobic cisplatin drug, which is a derivative of cisplatin with two benzoic groups attached, and MWCNT (Figure 16). The *in vitro* studies confirmed the stable entrapment of Platinum derivative particles in the nanotube and effective therapy in ovarian carcinoma cells.⁴¹¹

Another example is a three-element complex consisting of: Cisplatin, SWCNT, and epidermal growth factor (EGF) (Figure 17).

To reduce the low selectivity and direct the complex towards squamous cancer, EGF was added to the CNT and Cisplatin complexes. Without reducing the effectiveness of the therapy, it targets cells overexpressing EGFR, such as squamous cancer cells. This results in greater accumulation in these cells and a longer duration of action, which is confirmed by both *in vitro* and *in vivo* studies.^{412,413} The next study describes Cisplatin molecules inside SWCNT (Figure 18). The results of this study

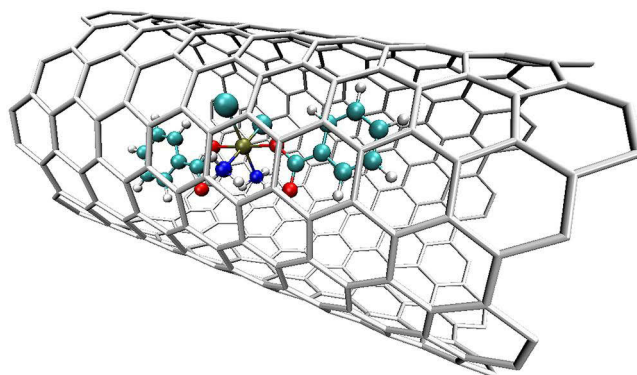


Figure 16 The structure of a complex of hydrophobic cisplatin drugs with two benzoic groups attached and MWCNT.⁴¹¹

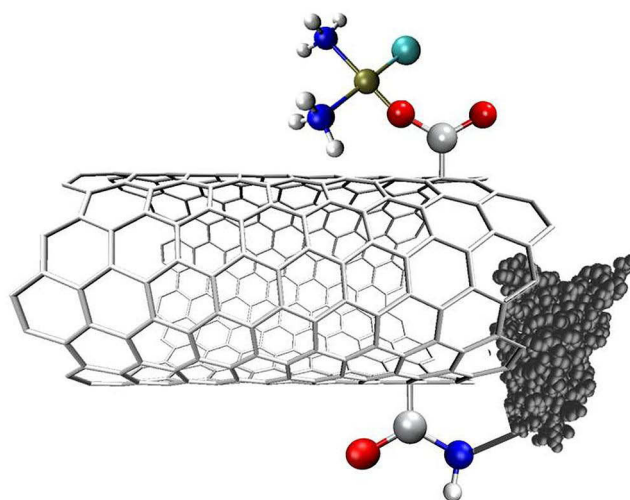


Figure 17 The structure of a complex of Cisplatin, SWCNT, and epidermal growth factor (EGF).⁴⁴³

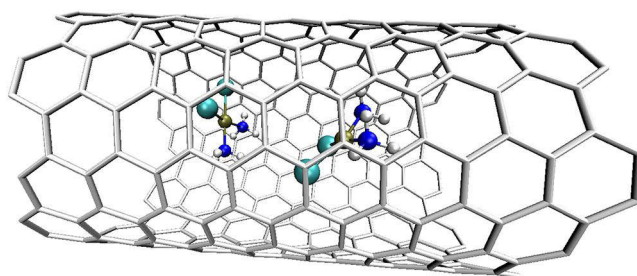


Figure 18 The structure of a complex of Cisplatin molecules inside SWCNT.^{444–446}

demonstrated that the Cisplatin complex in the nanotube reduced side effects by inhibiting non-specific, non-selective absorption compared to free Cisplatin. However, the complex was not as effective as free Cisplatin.^{414,415}

An interesting form seems to be the “Carbon Nanotube Bottle” complex, consisting of Cisplatin with MWCNT and Gold Caps (Figure 19).⁴⁴⁰

The study was designed so that the caps were made of alkanethiols combined with gold nanoparticles (GNP), protecting the open ends and protecting Cisplatin from a premature release. Only at low pH, ie the pH that occurs within the tumor, would it open and release the active substance. However, this significantly limited drug release once it reached the tumor, as in vitro studies showed that GNPs were end-blocked and approximately 40% of cisplatin was not released within the first hour.⁴³⁸ Another in vitro test was the complex of Cisplatin with ultrashort SWCNT and Pluronic F108 (Figure 20).^{416–418}

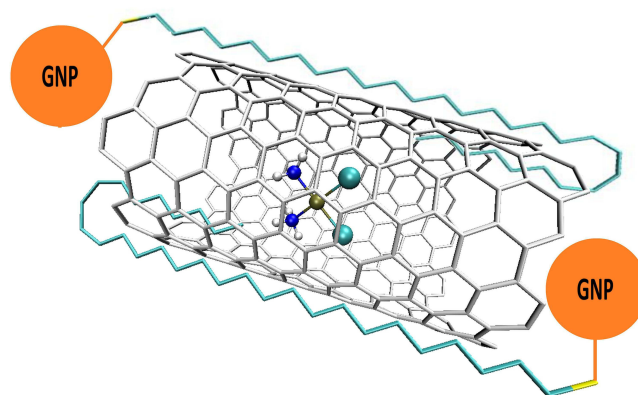


Figure 19 The structure of a complex of Cisplatin with MWCNT and Gold Caps.⁴⁴⁰ The abbreviation GNP represents gold nanoparticles.

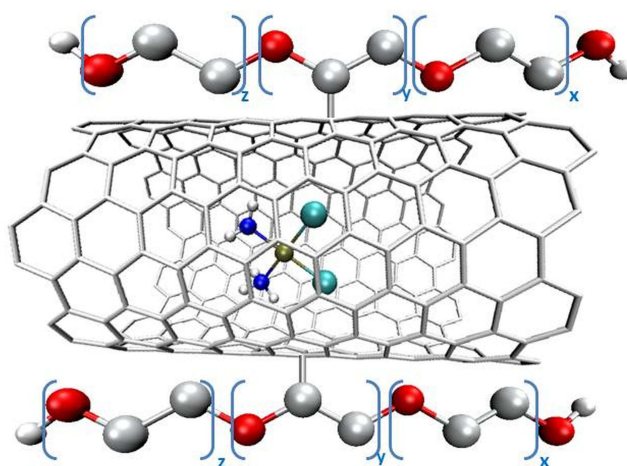


Figure 20 The structure of a complex of Cisplatin with ultrashort SWCNT and Pluronic F108.^{416–418}

Pluronic-F108 is a neutrally charged, non-cytotoxic surfactant commonly used for release control in carbon nanotubes. This ternary complex showed increased cytotoxicity against breast cancer cell lines after 24 hours compared to free Cisplatin.⁴¹⁶ The eighth and final in vitro study presents us this time with a complex consisting of Carboplatin and oxidized open-ended MWCN (Figure 21).

The results confirmed the lack of toxicity of the nanostructure and the effective, long-term release of Carboplatin particles, showing a maximum Platinum release of 68% on the fourteenth day. The results also showed higher cytotoxicity of compounds in nanostructures than free Carboplatin towards prostate, renal, and bladder cancer cell lines.⁴⁵⁰

Fullerenes

Fullerenes are allotropic forms of carbon, and their structure consists of sp^2 carbons connected by single and double bonds. Their structure resembles a symmetrical cage of various sizes and shapes. The most popular fullerene is fullerene C_{60} (Figure 22), which consists of 12 pentagons and 20 hexagons, and resembles a sphere in shape.⁴⁵

Fullerenes properties resemble hydrophobic compounds, for which they have a high affinity. Additionally, thanks to these properties, they have good penetration through cell membranes and significant biological activity.⁴⁵³ Fullerenes also easily react with electron-rich molecules and are able to bind other compounds using physical and chemical bonds or electrostatic interactions.^{410,454,455} The structure of fullerenes can be modified to increase their binding capacity.⁴⁵³ The specific structure allows them to bypass traditional drug resistance mechanisms.⁴⁵⁶ As shown by in vivo studies (Figure 23), fullerenes do not exhibit toxicity while maintaining strong antioxidant properties as free radical scavengers.⁴⁰⁸ C_{60} fullerene

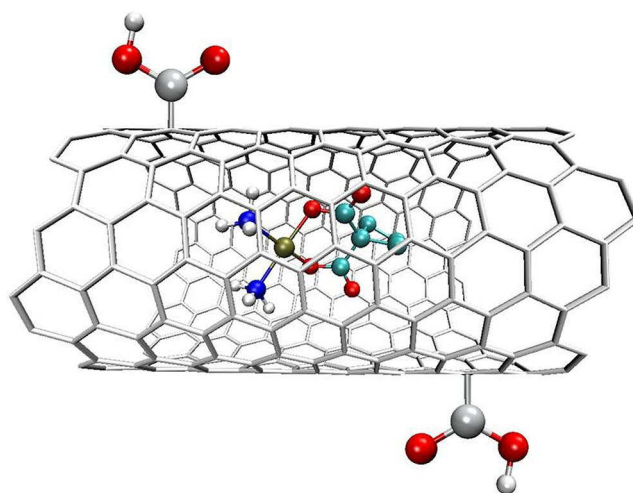


Figure 21 The structure of a complex of Carboplatin and oxidized open-ended MWCN.^{416,448,449}

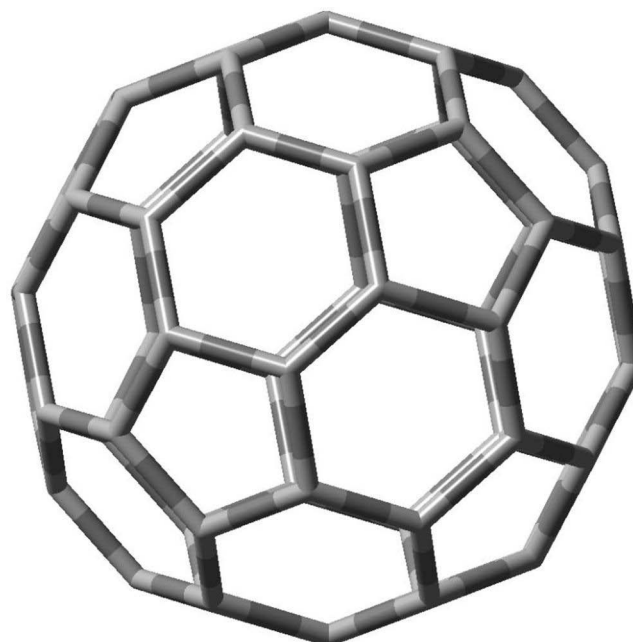


Figure 22 The structure of fullerene C₆₀.⁴⁵²

derivatives penetrate plasma membranes and concentrate inside cancer cells, which makes them suitable for the transport of Platinum-derived drugs.^{119,120,132,185,239,258,409,415,419}

In vitro studies have shown that C₆₀ fullerene nanoparticles in complexes do not cause DNA strand breaks while maintaining the cytotoxic properties of Cisplatin.⁴⁰⁸ Other studies have shown a greater cytotoxic effect of the complex compound on lung cancer cells compared to free Cisplatin, as demonstrated by IC 50 values, although lower after treatment for 48 and 72 hours.⁴¹⁰ The nano complex also promotes cell penetration and accumulation inside cancer cells, and thus intensifies the toxic effect inside cancer cells, consequently leading to apoptosis.⁴¹⁰ Studies on T-lymphoblastic leukemia cells showed that the fullerene complex with Cisplatin induces a statistically significant increase in the number of dead cells compared to Cisplatin alone.⁴⁰⁹

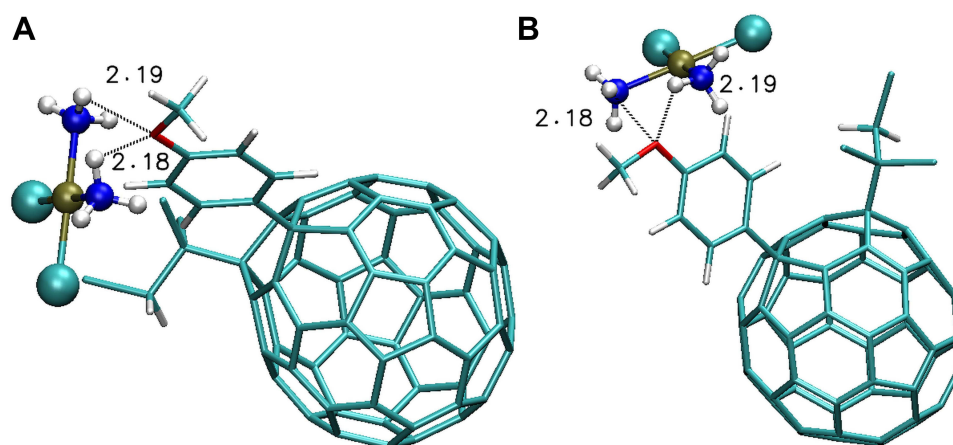


Figure 23 The examples of complex of functionalized fullerene C_{60} with Cisplatin.⁴²⁰

Rhombellans

Rhombellans are new theoretical nanostructures described for the first time in 2018 by Diudea, characterized by the fact that they are built in such a way that all strong rings are rhombuses, and some of them create propellant structures (tricyclo[1.1.1.01,3]pentane).^{457,458} They are synthesized from [1,1,1] propellane, which contains only triangles.²⁶⁵ As Diudea describes, Rhombellans have the following properties:

1. all strong rings are rhombuses;
2. vertex classes consist only of unconnected vertices;
3. the Omega polynomial has one term: $1X^{|E|}$;
4. the line graph of the parent graph has a Hamiltonian perimeter;
5. they contain at least one complete bipartite subgraph $K_{2,3}$ or the smallest $rb_{1.5}$ $rb_{1.5}$.⁴⁵⁹

Quantum calculations at the B3LYP/6-31G level of theory confirmed that the syntheses are energetically feasible.⁴⁵⁹ Studies on the properties of ADME (absorption, distribution, metabolism, and excretion) confirmed the properties of Rhombellanes as nano transporters delivering to the target site.^{261,263,265,270,275,421}

A comparative study on the structure of C_{60} fullerenes and Rhombellanes shows a significantly higher affinity of both Cisplatin⁴²⁰ and Carboplatin⁴¹⁹ to fullerenes than to Rhombellanes (Figure 24). Even though Platinum-derived compounds formed more bonds with Rhombellanes, they were of lower quality.⁴¹⁹ However, the affinity of Platinum

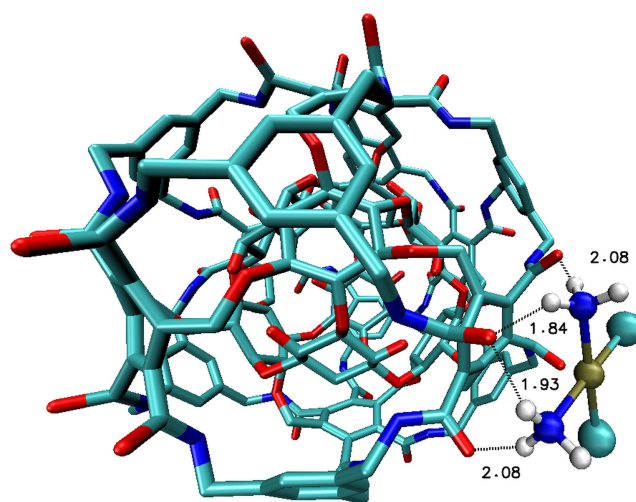


Figure 24 The structure of a complex of Rhombellane with Cisplatin.⁴²⁰

derivatives is so high that they can form complexes with both fullerenes and Rhombellanes. Comparing Cisplatin and Carboplatin, the affinity values for Carboplatin are much higher. As a result, Carboplatin can easily form complexes with these nanostructures.⁴²¹

Others Nanostructures

Micelles

Micelles are colloidal nanoparticles that are formed in an aqueous environment using amphiphilic copolymers or surfactants when the critical micellar concentration is exceeded.^{289,458} Micelles are excellent drug carriers because, due to their smaller size below 100 nm in diameter, they actively avoid RES and renal exclusion. They can even passively increase the penetration of the endothelial barrier in the area dominated by the tumor. Hydrophobic drugs become trapped in the innermost central region, resulting in increased water solubility, reduced toxicity profile, tumor cell-specific aggregation, and reversal of drug resistance, ultimately improving the therapeutic efficacy and bioavailability of poorly water-soluble drugs. Additionally, circulation time can be extended by adding a hydrophilic coating that prevents vesicular uptake.⁴⁶¹

Hydrogels

Hydrogels are a three-dimensional polymer mesh that retains a significant amount of water in its fibers.^{462,463} It is a system of a binary polymer solution that has a cross-linking agent. Hydrogels have gained much attention over the past three decades because they possess various unique features that are useful in biomedical applications. At room temperature, hydrogels exist as a solution, but when they reach body temperature, they transform into a gel. The main mechanism of the anticancer gel form is the creation of a drug reservoir from which the drug gradually penetrates. Hydrogels inhibit the formation of cancer, including lung cancer, and at the same time extend the life of the body.⁴⁶⁴

Nanoemulsions

Nanoemulsions are water-in-oil (w/o) or oil-in-water (o/w) droplets with an average radius of 10–100 nm that are translucent or transparent and exhibit a stable thermodynamic profile. This nanostructure is created by dispersing two immiscible phases: the water phase in the oil phase, and is maintained by reducing the interfacial tension using various surfactants and co-surfactants.⁴⁶⁵ This structure makes nanoemulsions excellent nanocarriers for hydrophobic and lipophilic chemotherapeutics. In addition, nanoemulsion helps in reducing hepatic bypass, inhibits drug degradation in an abnormal environment, eliminates P-glycoprotein efflux, facilitates penetration of mucous membranes, and thus improves the systemic availability of chemotherapy.⁴⁶⁶

Quantum Dots (QDs)

These are the smallest of all nanostructures (3–30 nm) made of semiconductor materials. QDs can be modified by coating with polymers that improve solubility and absorption.⁴⁶⁷ The biggest problem associated with the clinical use of QDs is the potential cytotoxicity.⁴⁶⁸ This problem is according with their structure which contains inducing cytotoxicity metal atom.⁴⁶⁹ QDs have been used in molecular profiling and cellular imaging of cancer.⁴⁷⁰ As proven by in vitro studies on lung cancer cell lines, conjugating Erlotinib with QD improves its effectiveness.⁴⁷¹ Additionally, QDs can be modified to control drug release in an acidic pH environment.⁴⁷²

Metal NPs (Nanoparticles)

Between structures contain metal atoms, used in oncology are iron nanoparticles,^{321,473} titanium dioxide nanoparticles,³²⁹ zinc oxide nanoparticles,⁴⁷⁴ cerium nanoparticles,⁴⁷⁵ silver nanoparticles⁴⁷⁶ or gold nanoparticles. The latter, due to their unique optical and surface properties, high biocompatibility, are easy to modify during synthetize and can be coated with a large number of molecules, including drugs used in chemotherapy.^{477–479}

Magnetic Nanostructures

Nanostructures that can be detected and manipulated using magnetic fields. Most often, they have sizes ranging from 10–200 nm and a neutral surface charge, which is needed to extend the circulation time.^{480,481} In recent years, they have been used in diagnosis and treatment of lung cancers.^{482–484} However, they exhibit high toxicity. Magnetic nanostructures

can interfere with cellular metabolism and cause side effects by producing reactive oxygen species and increasing for example the concentration of free iron by metabolizing iron oxide nanoparticles.^{381,485}

Conclusions

To sum up, Platinum compounds have been approved for treatment since 1978, and despite the fact that knowledge about these drugs has grown significantly and many newer anticancer drugs and various anticancer therapies have entered the market, virtually unchanged Platinum compounds have not fallen out of use and are still among the most popular compounds used in certain types of cancer. However, numerous problems associated with therapy with Platinum derivatives have been noticed. Firstly, increasing resistance to Platinum-derived compounds, and secondly, high toxicity resulting from low selectivity. The most popular solutions to these problems are complex therapy, targeted therapy, and conjugation of Platinum derivatives with nanostructures. Theoretical research, as well as in vitro and in vivo studies, on nanostructures are optimistic and prove that in the future we will be able to allow new, better forms of Platinum-derivative drugs for treatment, which will accumulate better at the site of the tumor, cause fewer side effects for the body, and limit the phenomenon of resistance. The presence of nanostructures can protect Platinum-derived drugs from reacting with substances in the bloodstream (eg originating from food and drugs, such as B vitamins or proteins), thus reducing the therapeutic effect. However, despite numerous studies on single complexes of nanostructures, there is still a lack of comparative studies that would compare different complexes of Platinum compounds and nanostructures under the same conditions.

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