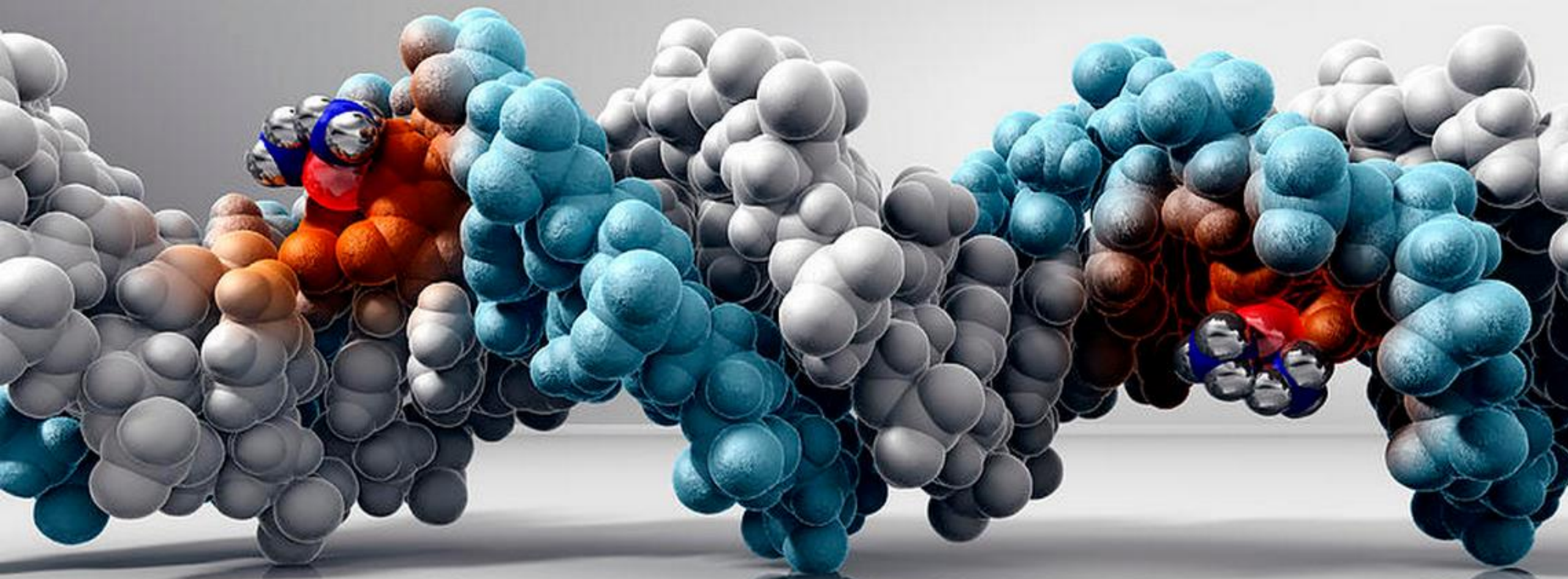


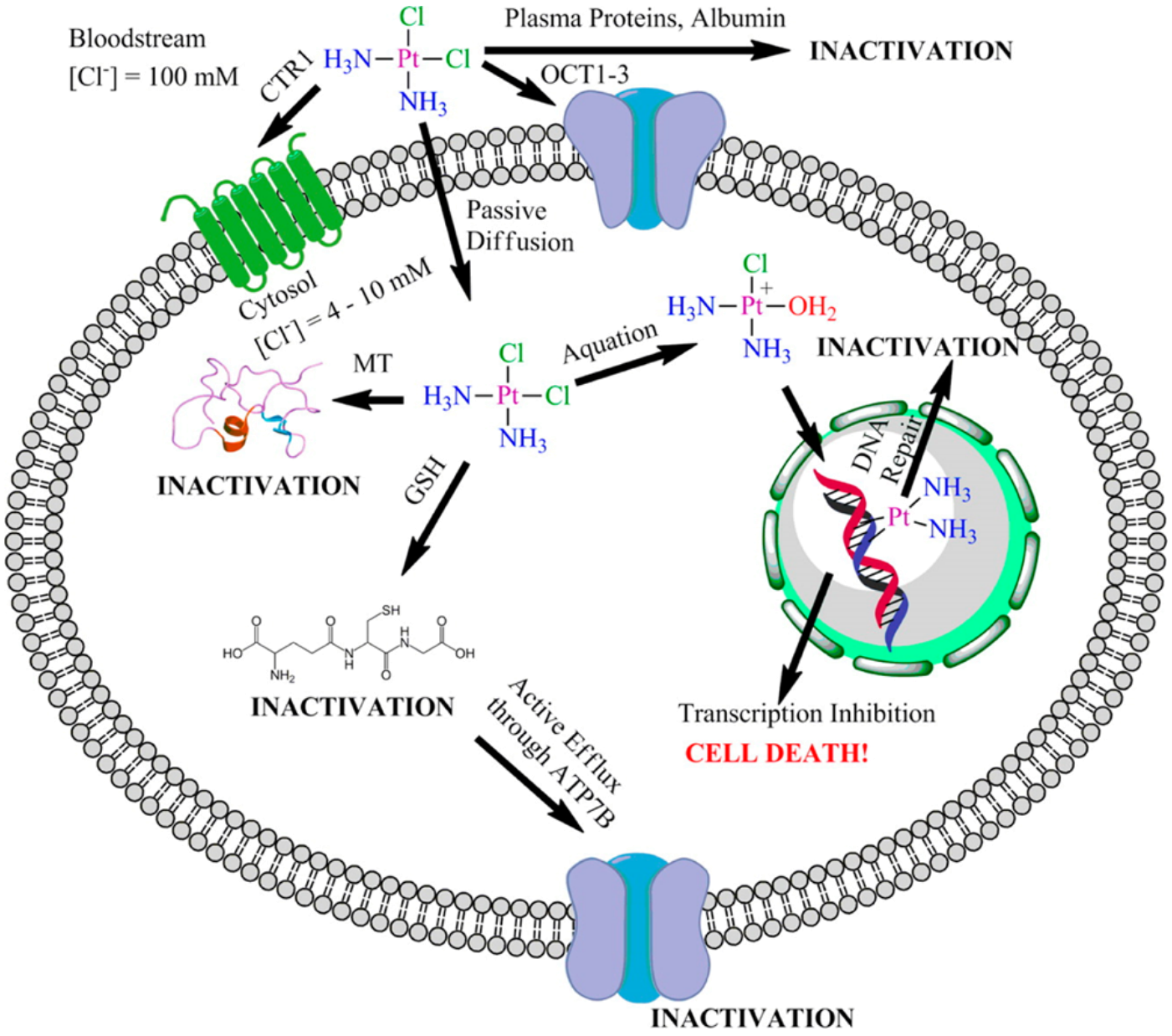
# Cisplatin and related antineoplastic drugs

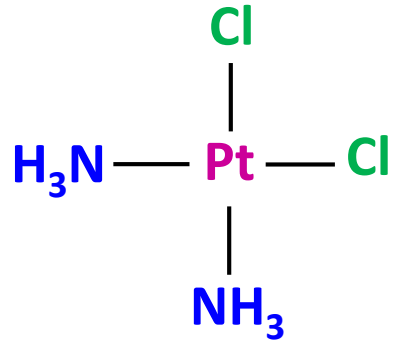
# Main pillars of cancer treatment

Chemotherapy Surgery Radiation therapy

The term ‘‘chemotherapy’’ refers to the use of any chemical agent to stop cancer cell proliferation. Chemotherapy has the ability to kill cancer cells at sites remote from the original cancer. Thus chemotherapy is referred to as systemic treatment.

Platinum compounds have been the treatment of choice for ovarian, testicular, head and neck, and small cell lung cancer for the past 20 years.


Bloodstream
[Cl⁻] = 100 mM
CTR1
Plasma Proteins, Albumin
INACTIVATION
OCT1-3
Passive Diffusion
Cytosol
[Cl⁻] = 4 - 10 mM
Aquation
MT
INACTIVATION
GSH
INACTIVATION
DNA Repair
Transcription Inhibition
CELL DEATH!
Active Efflux through ATP7B
INACTIVATION



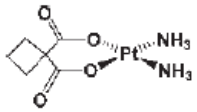
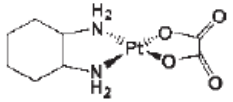
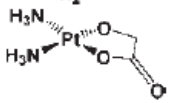
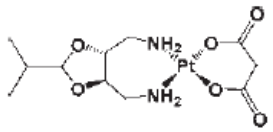
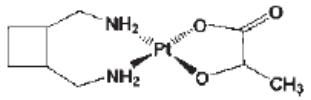
Cisplatin

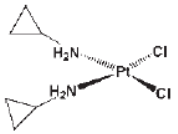
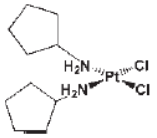
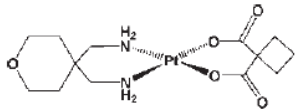
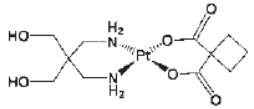
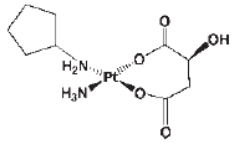
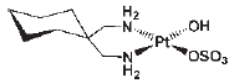
**Success of cisplatin**

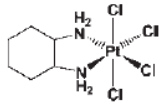
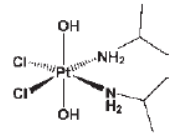
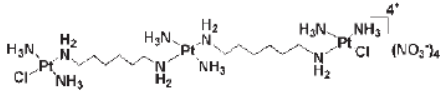
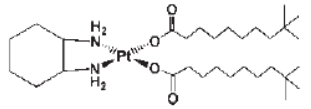
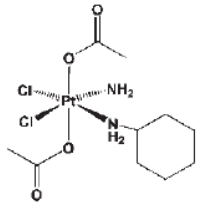
**Expansion of the family of platinum compounds.**

**Carboplatin and oxaliplatin** are registered worldwide and have been a major success in clinical practice.

**Nedaplatin** is used in **Japan** to treat head and neck, testicular, lung, ovarian, cervical, and non-small cell lung cancers. **Heptaplatin** is used in gastric cancer in **South Korea.** **Lobaplatin** is approved in **China** for the treatment of chronic myelogenous leukemia, metastatic breast, and small cell lung cancer.

| Compound | Structure | Use | Current state |
|---|---|---|---|
| Cisplatin |  | Head and neck, testicular, lung, ovarian, cervical, and non-small cell lung cancers | FDA approved |
| Carboplatin |  | Head and neck, testicular, lung, ovarian, cervical, and non-small cell lung cancers | FDA approved |
| Oxaliplatin |  | Colon cancer | FDA approved |
| Nedaplatin |  | Head and neck, testicular, lung, ovarian, cervical, and non-small cell lung cancers | Phase II |
| Heptaplatin |  | Gastric, head and neck cancer, small cell lung cancer | Approved in South Korea |
| Lobaplatin |  | Chronic myelogenous leukemia (CML), metastatic breast, and small cell lung cancer, esophageal, ovarian cancers | Approved in China<br>Phase II in USA |

| Compound | Structure | Use | Current state |
|---|---|---|---|
| JM-11 |  | Malignant disease | Abandoned |
| PAD |  | Leukemia | Failed in Phase I |
| Enloplatin |  | Refractory advanced ovarian carcinoma | Failed in Phase I |
| Zeniplatin |  | Ovarian cancer | Failed in Phase I |
| Cycloplatam |  | Ovarian and lung cancer | Failed in Phase I |
| Spiroplatin (TNO-6) |  | Ovarian cancer | Failed in Phase-II |

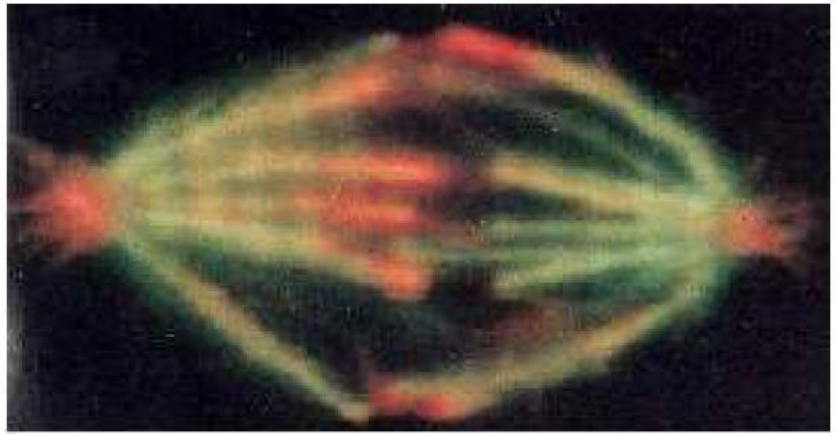
| Compound | Structure | Use | Current state |
|---|---|---|---|
| Ormaplatin (Tetraplatin) |  | Melanoma, sarcoma, leukemia and breast cancer, refractory diseases | Failed in Phase I |
| Iproplatin (JM-9) |  | Small cell carcinoma of the lung, ovarian, metastatic breast, and head and neck cancer | Phase II and Phase III |
| Triplatin tetranitrate (BBR-3464) |  | Ovarian, small cell lung and gastric cancer | Failed in Phase II |
| Aroplatin (l-NDDP) |  | Colorectal and kidney cancer, malignant pleural mesothelioma | Phase II |
| Satraplatin (JM-216) |  | Prostate cancer | Failed in Phase III |

The **clinical development of novel platinum compounds** has been somewhat **disappointing** in view of the promise shown in preclinical studies. The vast majority of platinum compounds synthesized for cancer therapy have been abandoned because of low efficacy, high toxicity, and/or low water solubility.

# A little history of cisplatin

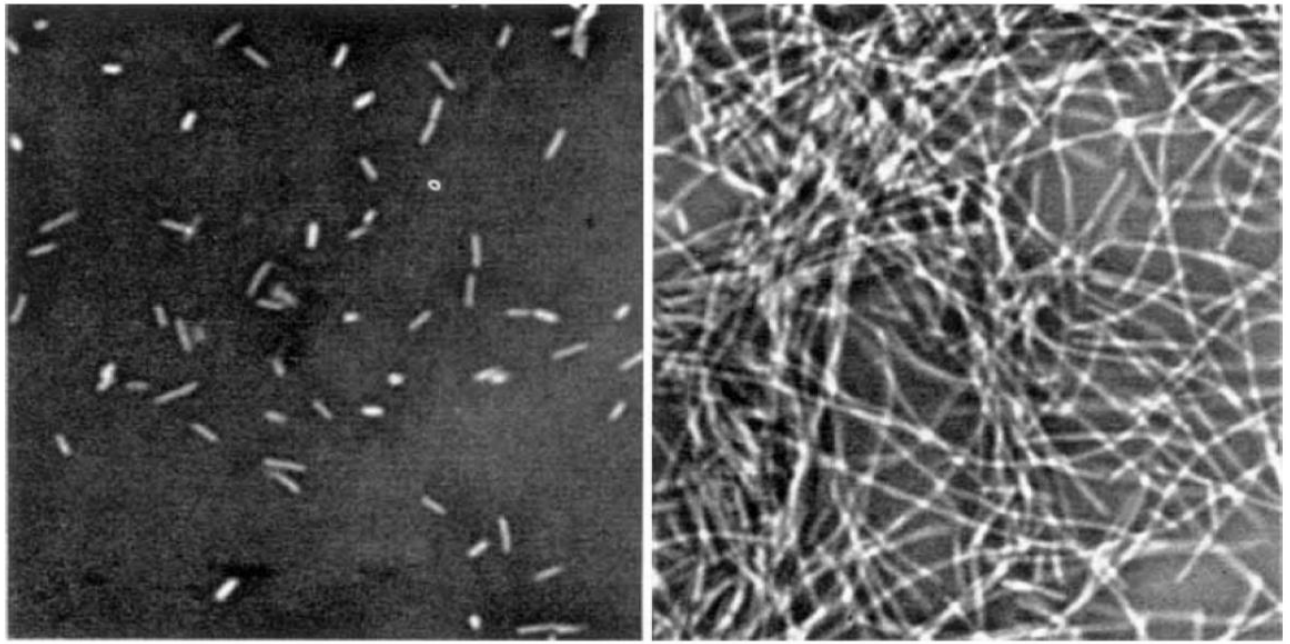
The compound cis-[$Pt(NH_3)_2Cl_2$] was first described by Michele Peyrone in 1845, and known for a long time as Peyrone's salt. The structure was deduced by Alfred Werner in 1893.

The **cytostatic effect** of *cis*-diamminedichloridoplatinum(II), “cisplatin”, a squareplanar complex due to the $d^8$ configuration of the metal, was serendipitously discovered by B. Rosenberg in the 1960s.
Studying the influence of weak alternating currents on the growth of *E. coli* bacteria, he used **“inert” platinum electrodes**.



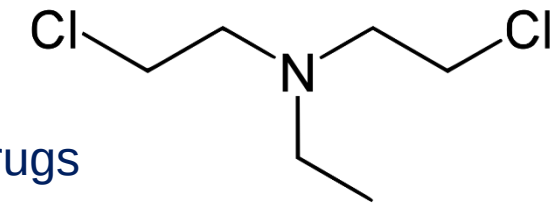
The result of his experiments was an inhibition of cell reproduction without simultaneous inhibition of bacterial growth, which eventually led to the formation of **long, filamentous cells**.

Normal bacterial growth



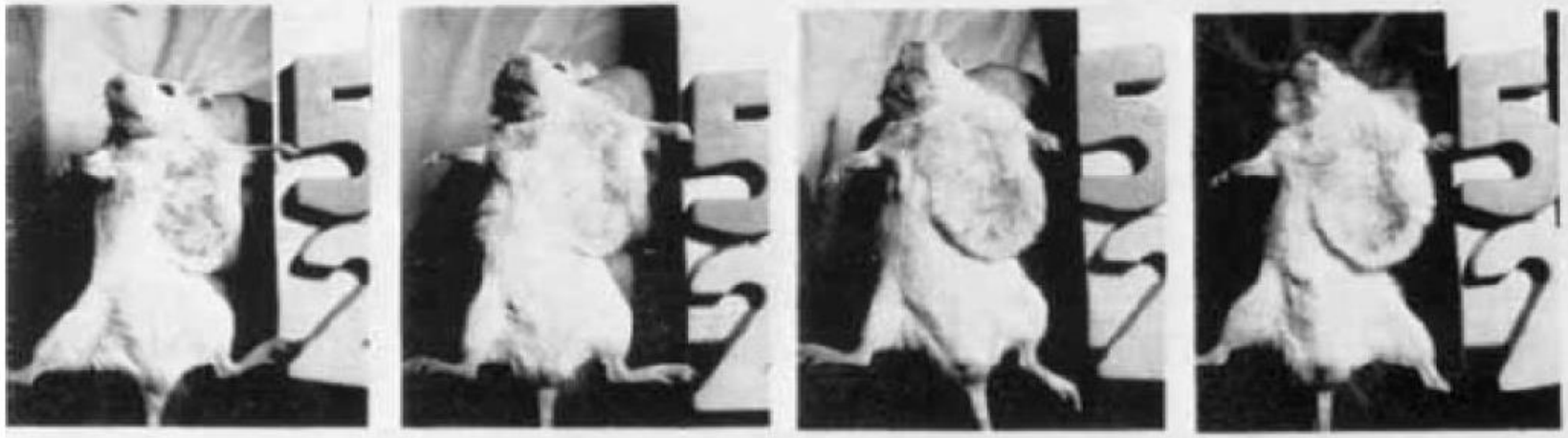
Filamentous bacterial growth induced by 10 ppm of cisplatin

In the course of subsequent, more detailed studies, it was found that it was not the electric current itself but trace amounts of *cis*-configured chlorido complexes such as, resulting from an oxidation of the platinum electrode, that were responsible for this biological effect.




This effect is characteristic of nitrogen mustards which where used as antineoplastic drugs

CONTROL SARCOMA 180



DIED - day 21

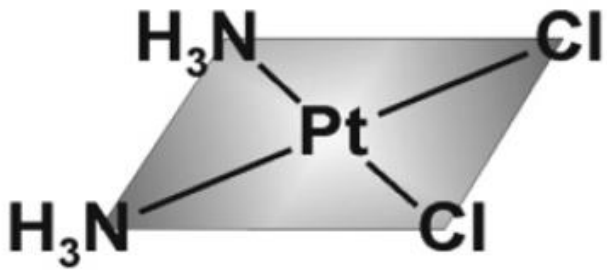
day 8 day 12 day 16 day 20

TREATED - SINGLE INJECTION CIS - $Pt(II)(NH_3)_2Cl_2$ - 8 mg/kg - DAY 8

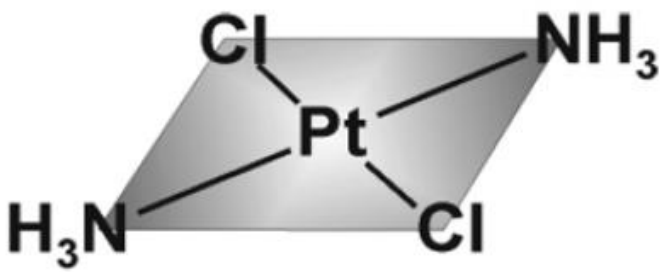
day 8 day 12 day 16 day 20 day 36

Like gold, **oxidized platinum forms very stable complexes with halides and pseudohalides**, and the otherwise very noble metals are thus much more easily oxidized in the presence of such ligands.

In the **presence of chloride and ammonium/ammonia** as components of typical buffered culture media, **sufficient material is apparently oxidatively dissolved from the platinum electrode**; the potential for the formation of the primarily resulting complexes $[PtCl_{4,6}]^{2-}$ from Pt is about 0.7V.



*cis-*



*trans-*

Used in therapy

Even more active *in vitro*, but lacks of efficacy *in vivo*

Cisplatin has been approved as a drug since about 1978

is still being used either **alone or in combination with other cytostatic agents** such as bleomycin, vinblastin, cyclophosphamide and doxorubicin against testicular and ovarian cancers, and against bladder, cervical and lung tumors and tumors in the head/neck area.

Over the years, the prospects for a complete cure of testicular and bladder cancer have vastly improved (>90%; → cyclist Lance Armstrong), mainly due to the use of cisplatin and other platinum-containing drugs.

Side effects:
**Tinnitus, neuropathic pain,**
**kidney and gastrointestinal problems**, including nausea,
-attributed to the inhibition of enzymes through coordination of the heavy-metal platinum to sulfhydryl groups in proteins-

Accordingly, a treatment with sulfur compounds, such as sodium diethyldithiocarbamate (19.4) and thiourea, and subsequent diuresis may counteract these symptoms.

In contrast to many other cytostatic agents, however, cisplatin causes only **minor, reversible damage to the spinal region**.

The aim of the development of second- and third-generation analogues of cisplatin is to obtain drugs with **broader applicability**, **lower therapeutic dosage**, **reduced side effects**, **diminished therapeutic resistance** (a number of cisplatin-resistant cell lines have meanwhile developed) and **oral administration** (cisplatin has to be injected)

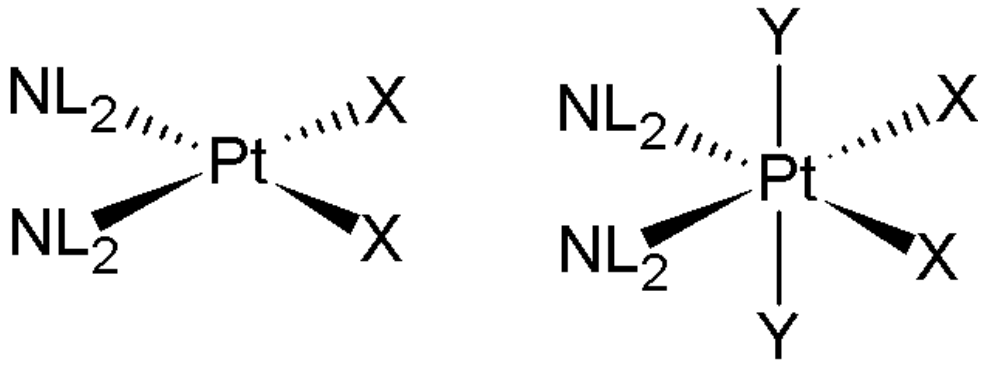
## Drug design criteria

Both square-planar Pt(II) and octahedrally configured Pt(IV) complexes show cytostatic activity; however, that of the platinum(IV) compounds is usually lower. It has been assumed that the **"active" Pt(IV) complexes are reduced to Pt(II)** derivatives *in vivo*.

In general, continuous cytostatic activity has been found **only for compounds with *cis* configuration**; most but not all *trans* isomers seem to be ineffective.

Active complexes contain two non-leaving (NL) groups in *cis* positions and **two monodentate or one bidentate labile ligand**.

Amine ligands are the preferred NL groups; they must contain at least one N–H function and thus a possibility for hydrogen bond formation. The N−H bonds in coordinated primary or secondary amines can have several functions: they can facilitate the approach of the molecule to DNA and contribute to the base-specific formation and stabilization of the resulting adducts.



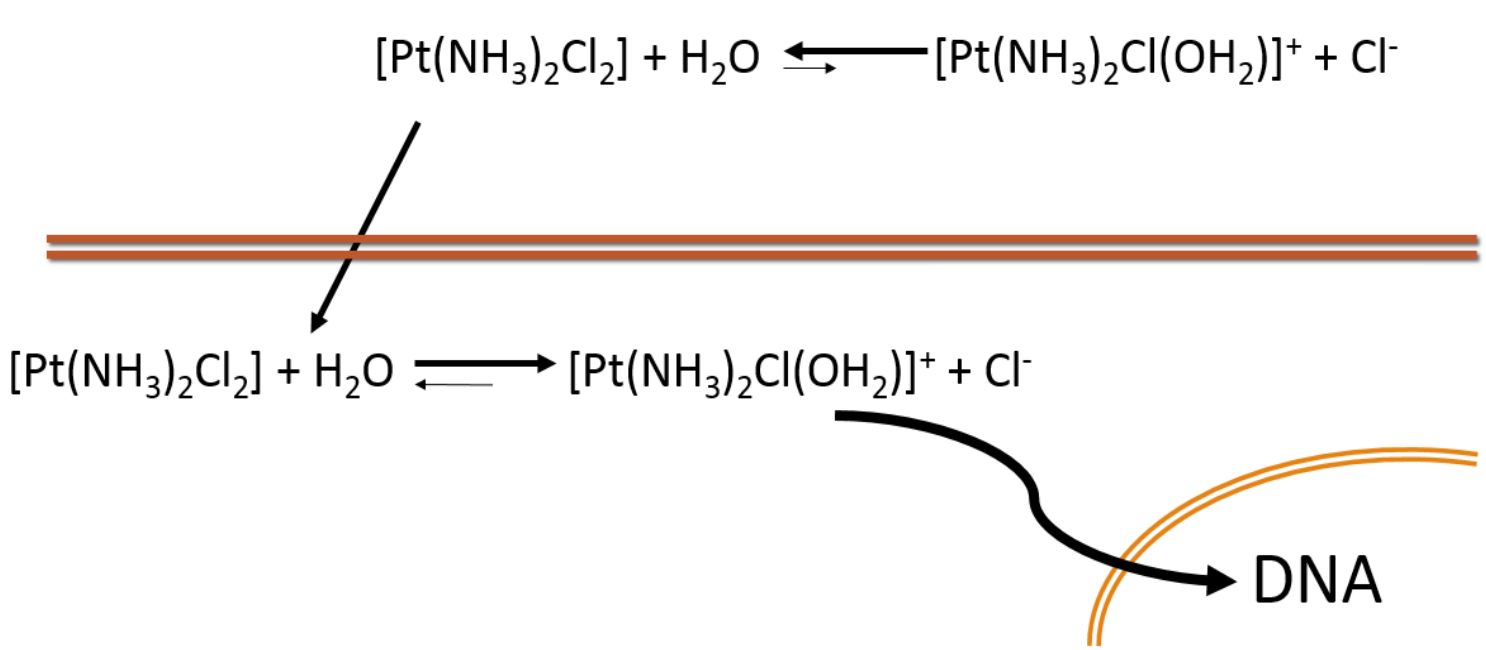

The ligands, X, corresponding to the general formula *cis*-[Pt(II)$X_2(NL)_2$] for divalent and *cis*-[Pt(IV)$X_2Y_2(NL)_2$] for tetravalent platinum are typically anions which exhibit an intermediate bond stability with platinum and are thus exchangeable on a therapeutical/physiological timescale. **Examples for X are halides, carboxylates (often as chelating ligands), sulfates, aqua and hydroxido ligands**.

*Trans*-positioned OH− groups are often used for Pt(IV) compounds, in order to increase their water solubility; with a maximum of 0.25 g per 100 mlH2O, **cisplatin itself is not particularly soluble**.

Complexes **with very labile ligands X are toxic**, while **very inert Pt−X bonds** render the corresponding substances **inactive**.

As a rule, **active complexes are neutral and may thus initially penetrate cell membranes more easily than can charged compounds**.

After passive transport of neutral cisplatin through the cell membranes of different organs and tumor cells, it is **rapidly hydrolyzed** due to the markedly **lower chloride concentration in intracellular space**




$$[PtCl(NH_3)_2(H_2O)]^+ \rightleftharpoons [PtCl(NH_3)_2(OH)] + H^+$$

$$[PtCl(NH_3)_2(H_2O)]^+ + H_2O \rightleftharpoons [Pt(NH_3)_2(H_2O)_2]^{2+} + Cl^-$$

$$[Pt(NH_3)_2(H_2O)_2]^{2+} \rightleftharpoons [Pt(OH)(NH_3)_2(H_2O)]^+ + H^+$$

$$[Pt(OH)(NH_3)_2(H_2O)]^+ \rightleftharpoons [Pt(OH)_2(NH_3)_2] + H^+$$

Within cells, about 40% of the platinum is present as *cis*-$[Pt(NH_3)_2Cl(H_2O)]^+$.

$H_2O$ is a much better leaving group with respect to Pt(II) than is Cl−; it is thus assumed that ***cis*-$[Pt(NH_3)_2Cl(H_2O)]^+$ is a particularly active form** of the cytostatic agent.

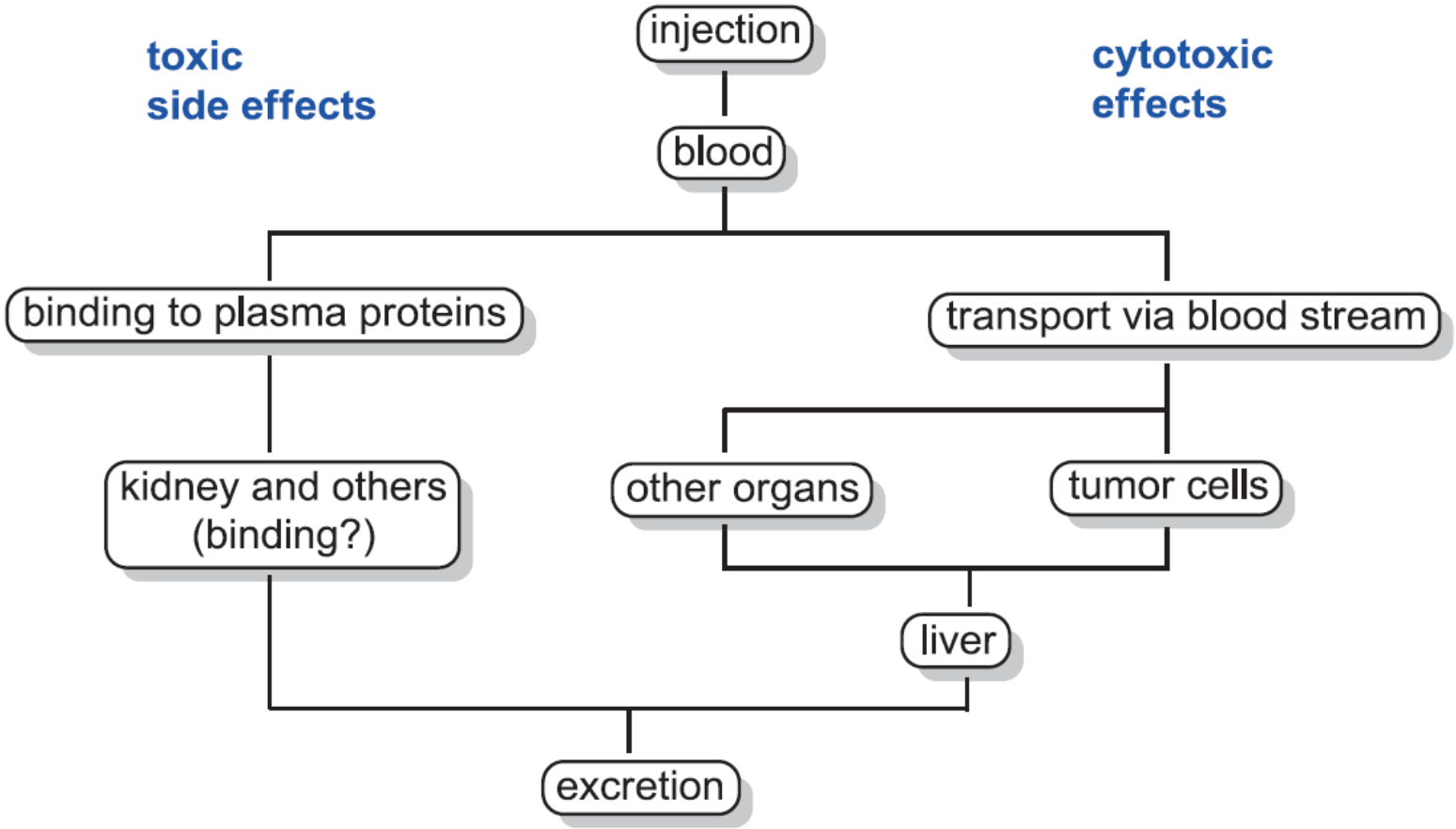
The positive charge of this substituted complex supports such an assumption, as it will be more likely to approach and coordinate with the negatively charged DNA.

Tumor cells are distinguished from normal body cells by **the loss of genetic control of their lifespan**.

Likewise, their feedback **mechanisms with regard to the existence of neighboring cells are impaired, which leads to the uncontrolled growth of tumor tissue**. In normal cells, these processes are restrained and regulated by proto-oncogenes; cancer may thus result from changes of these genes or their expression. According to this basic concept of carcinogenesis, **cisplatin is believed to exert its cytostatic effect primarily through coordination with DNA in the cell nucleus**, while reactions in other regions (e.g. with serum proteins) cause undesired side effects.

Platinum retention times are different in different organs, decreasing in the order **kidney > liver > genitals > spleen > bladder > heart > skin > stomach > brain**.

After interaction with the DNA in the cells of these organs, the degradation products are excreted via the liver and kidney.



Interactions of metal ions or metal complexes with nucleic acids generally play an important role:

in sustaining the conformation of the tertiary structure of polyelectrolytes such as DNA or RNA through electrostatic effects;

in the nucleic acid metabolism, particularly phosphoryl transfer (nuclease and polymerase activity);

in the regulation, replication and transcription of genetic information

in efforts directed at specific DNA cleavage with synthetic probes (restriction enzyme analogues);

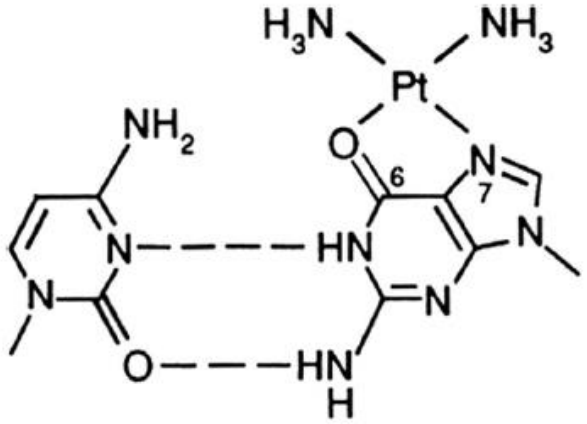
in **metal-induced mutagenesis**.

Replication and genetic transcription may be impaired with regard to **their accuracy ("fidelity") or their ability to recognize and repair defective sites**.

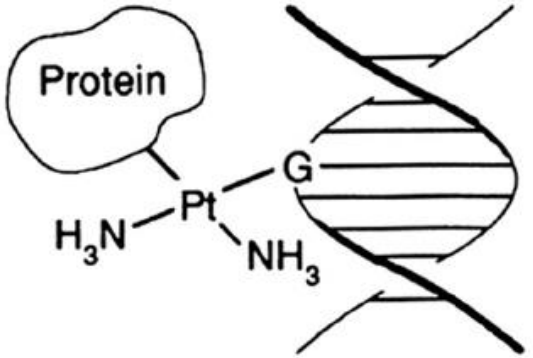
A significant aspect regarding the mutagenicity of compounds even of the essential metals is their behavior towards discriminating mechanisms such as the membrane barrier protecting the chromosomal area.

**Cisplatin can also cause mutations if present in higher concentrations.**

A coordinatively unsaturated metal complex fragment **with two open sites in *cis* position may bind in different ways to double-stranded DNA**.

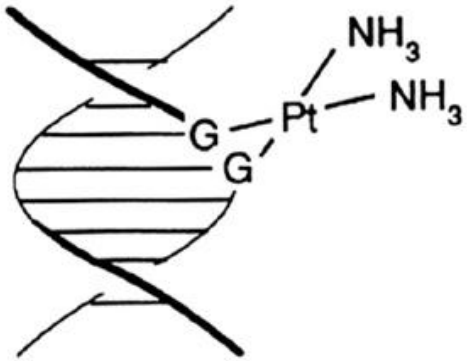



chelate coordination
to a guanine base

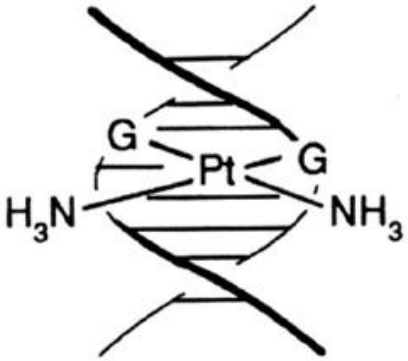



DNA-protein cross-linking

Since complexes
with only one labile ligand, such as chlorido(diethylenetriamine)platinum(II) $[Pt(dien)Cl]^+$
are therapeutically inactive, **the monofunctional platinum species presumably serve only as intermediates**.




1,2-intrastrand cross-linking

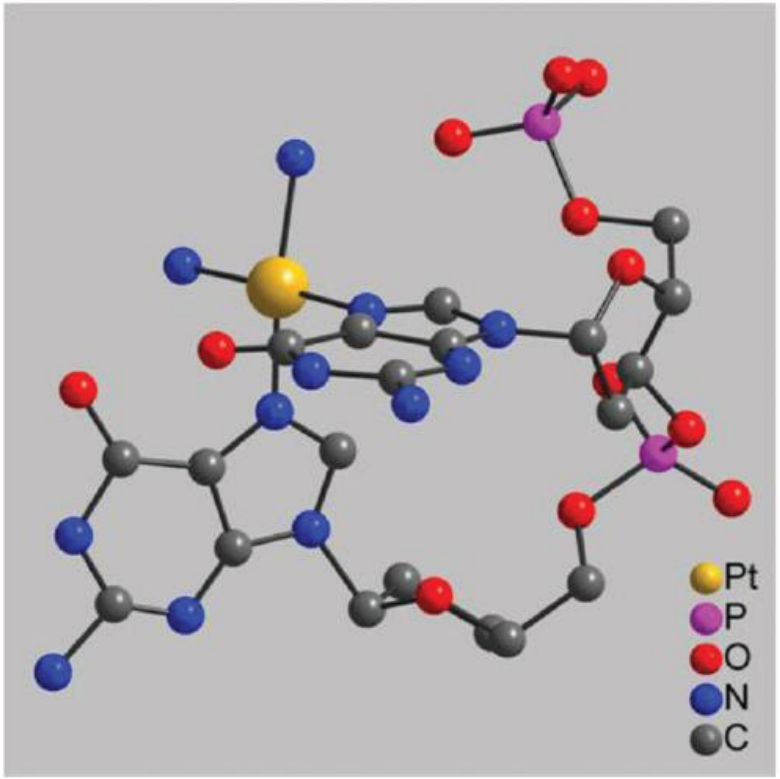



interstrand cross-linking

Experiments have shown that **the chelate complex formation with O6 and N7 of a free guanine base is possible in principal but is not favored** within the DNA double helix.

Interstrand crosslinking and protein–DNA interactions also make only minor contributions to the overall platinum/DNA adduct formation in the case of $[Pt(NH_3)_2]^{2+}$, the situation (and the cytostatic spectrum) being different with more recently developed bi and trinuclear complexes.

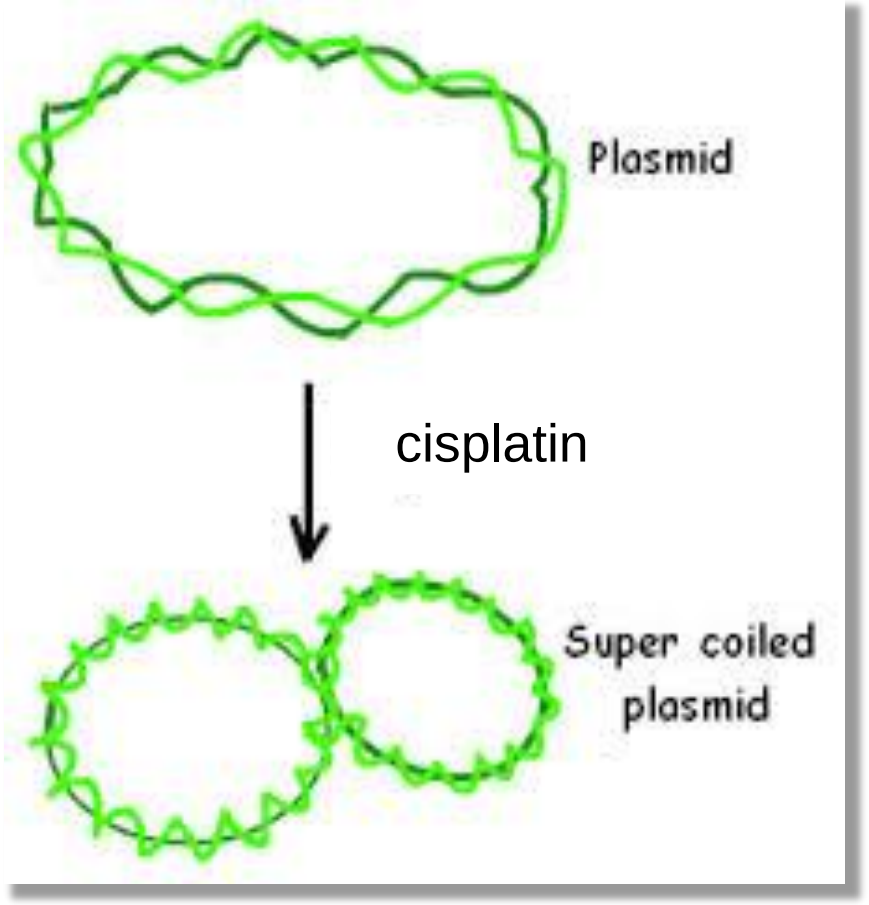
Most of the retained diammine platinum(II) forms bonds with two neighboring N7-coordinated guanosine (G) nucleotides on the same DNA strand (1,2-intrastrand d(GpG) crosslinking; d: deoxy form of ribose; p: phosphate); 1,2-intrastrand d(ApG) crosslinking (each via N7) has also been observed



Cisplatin can modify DNA morphology

First studies on cisplatin binding to DNA were about circular plasmids

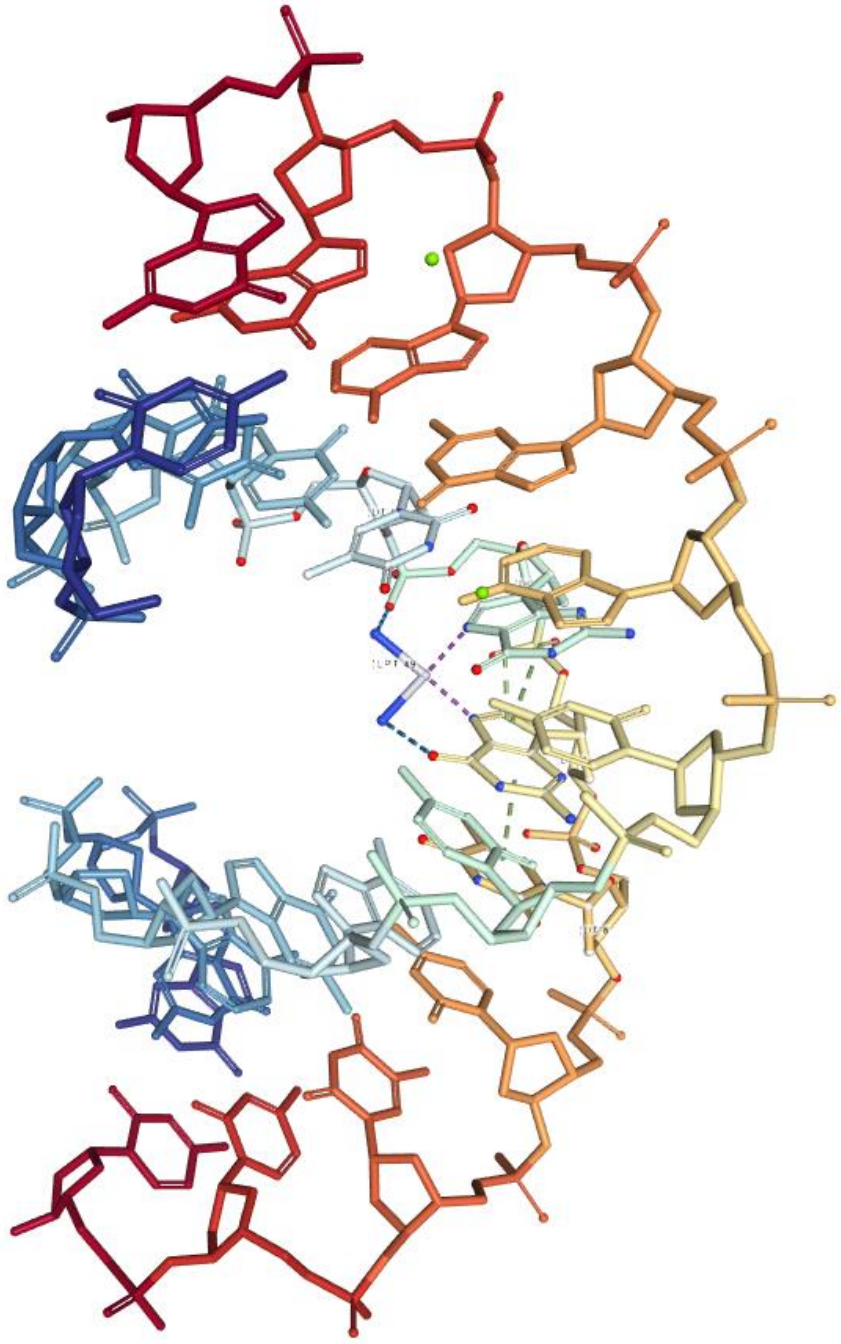
=> Supercoiling of the plasmid



The structural changes in DNA following coordination of $[Pt(NL)_2]^{2+}$ fragments have been quantitatively assessed by various physical measurements of single- or doublestranded DNA and of DNA fragments.

In the x-ray structure of *cis*-$[Pt(NH_3)_2\{d(pGpG)\}]$, which represents the $[Pt(NH_3)_2]^{2+}$-adduct to single-stranded DNA, the square planar platinum center is surrounded by two *cis*-positioned $NH_3$ ligands and two N7 nitrogen atoms of the two guanine bases.

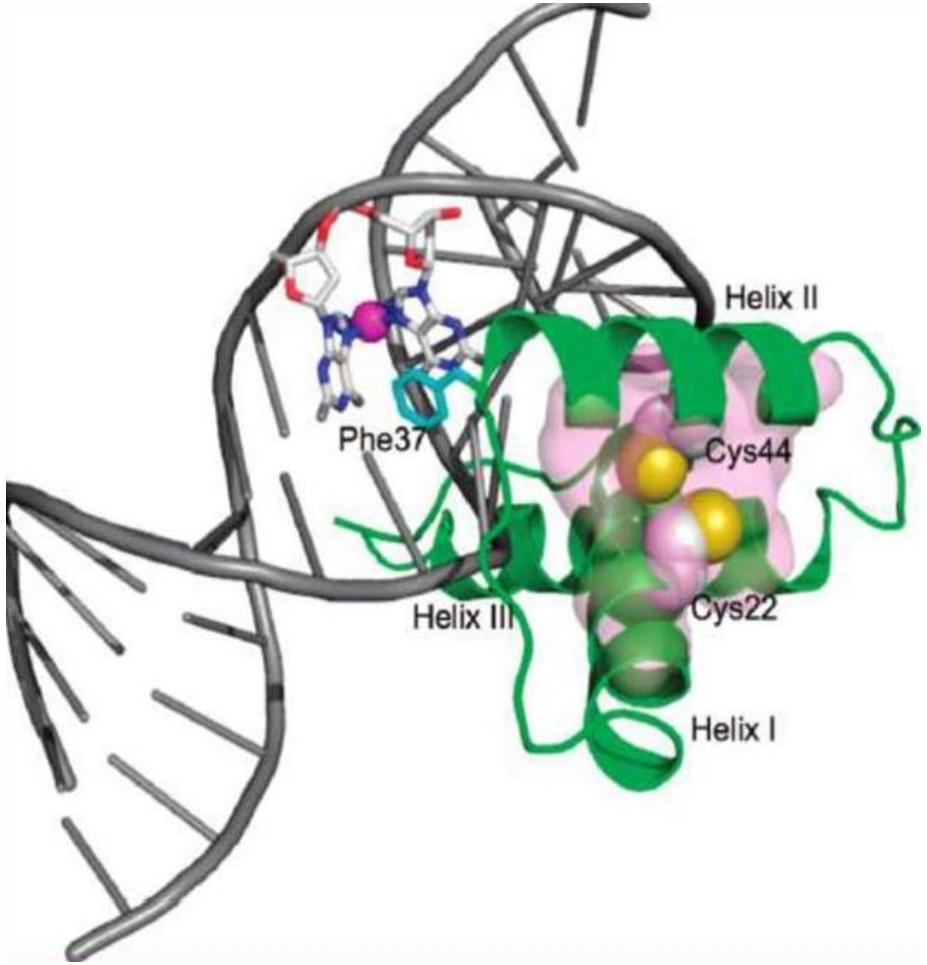
While the **nucleobases are situated nearly parallel to each other (stacking) in an intact DNA**, they **form a dihedral angle of about 80◦ in this model for platinum-coordinated DNA**, and the consequence is a **significantly perturbed double-helix structure**

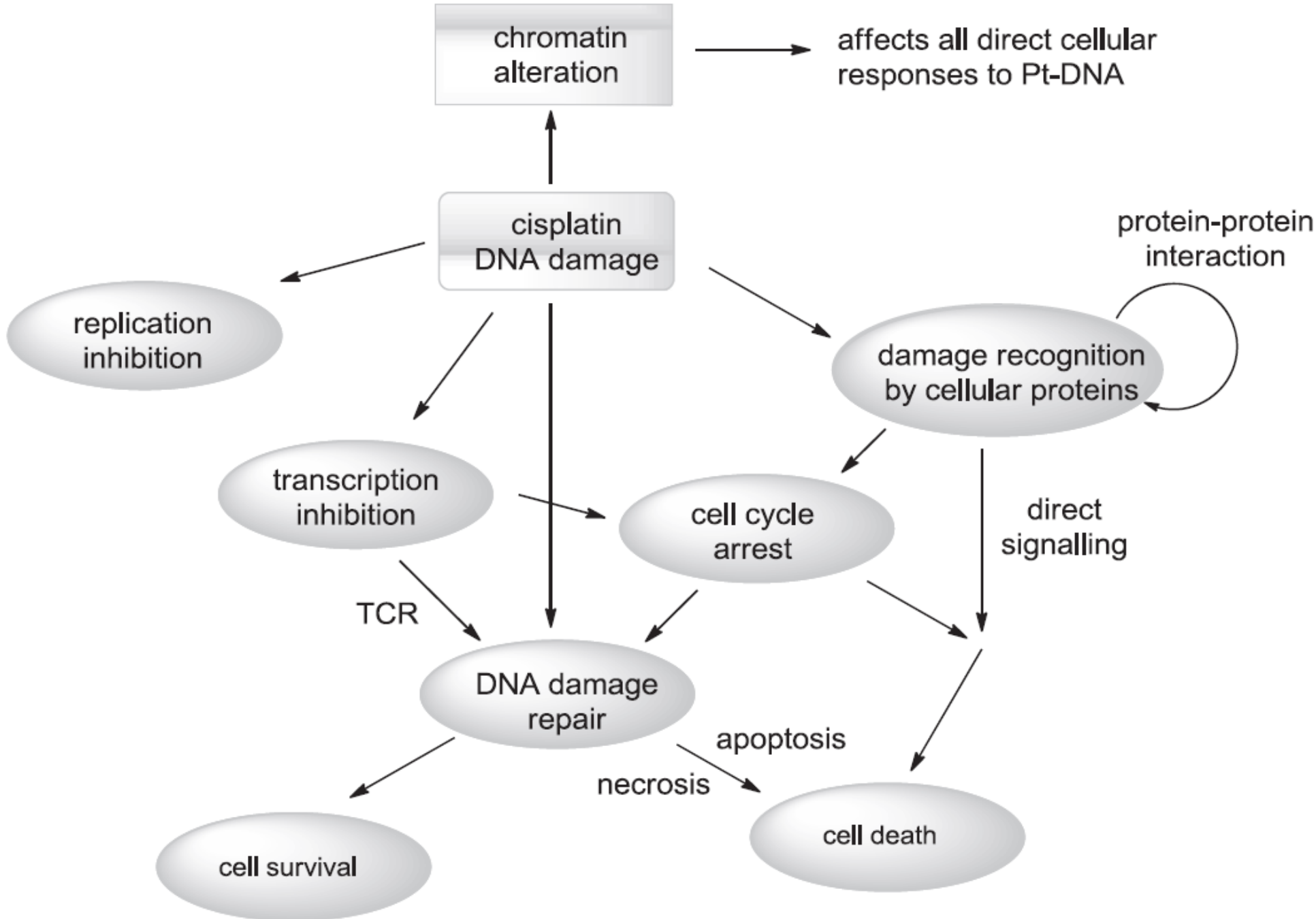


PDB =3LPV
X-ray crystal structure of duplex DNA containing a cisplatin 1,2-d(GpG) intrastrand cross-link

Of **importance for the cytotoxic behavior** are the consequences of the **distortions in the Pt-DNA adducts**. The adducts can **impede cellular processes such as DNA replication and transcription**, which require DNA strand separation. Furthermore, **the damage is recognized by several cellular proteins** (chromatin alternation), some of which are involved in DNA repair, including transcription-coupled repair (TCR).

The specific binding of a chromosomal “high-mobility group” (HMG-1) protein to *cis*-$[Pt(NH_3)_2]^{2+}$-containing DNA suggests a flawed genetic information transfer, either via altered transcription or through faulty recognition and thus shielding from DNA repair processes




chromatin alteration
affects all direct cellular responses to Pt-DNA
cisplatin DNA damage
protein-protein interaction
replication inhibition
damage recognition by cellular proteins
transcription inhibition
cell cycle arrest
direct signalling
TCR
DNA damage repair
apoptosis
necrosis
cell survival
cell death