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RESISTANCE AND SENSITIVITY; COMPETITIVE MECHANISMS OF CISPLATIN

Maria Fareed Siddiqui* and Esha Sadiq

Centre for Research in Molecular Medicine (CRiMM), The University of Lahore, 1 km Defense Road Lahore, Pakistan

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Correspondence to Author:
Maria Fareed Siddiqui

Centre for Research in Molecular Medicine (CRiMM), University of Lahore, 1 km Defense Road Lahore, Punjab, Pakistan

E-mail:maria.pharmacist@gmail.com

ABSTRACT: In the battle against cancer, platinum drugs have contributed a lot so far but still the prerequisite is to mend their flaws e.g., resistance and reduced sensitivity. In addition to side effects, intrinsic and acquired resistance decreases the effects of cisplatin on cancer cells by lowering the formation of DNA adducts and subsequent DNA damage. Resistance against cisplatin includes; the increased DNA repair of cisplatin induced DNA adducts by MMR, NER pathways, increased tolerance, and interaction with cellular proteins instead of DNA resulting in cellular detoxification of cisplatin, and, decreased accumulation of drug due to abnormal role of efflux and influx pumps. With therapy of cisplatin survival pathways (Akt, MKPI) are also triggered, occasioning in the activation of NF-kb, XIAP that subsidizes to cisplatin resistance. Development of new platinum compounds that can combat with the intrinsic and acquired drug resistance would be the promising strategy in the cancer therapeutic field. Combination or adjuvant therapies of cisplatin with gemcitabine, etoposide, topotecan etc. have been shown to reduce the cellular resistance by upsetting the DNA repair pathways. Furthermore, use of kinase inhibitors along with cisplatin would hinders MAPK and other pathways that are usually actuated by oxidative stress prompted by cisplatin.

INTRODUCTION: Survival pathway; PI3K/Akt activation as a consequence of cisplatin DNA damage. Akt also known as protein kinase B is a serine/threonine protein kinase. Being significant proto-oncogene it participates in many cellular procedures and blocks apoptosis through promoting cell survival and proliferation. There are three AKT isoforms which are resultantly obtained from discrete genes (AKT1/PKBα, AKT2/PKBβ and AKT3/PKBγ). Akt is an inactive cytosolic protein which is activated by receptor tyrosine kinases, survival and growth factors or by other stimuli that induces its recruitment towards plasma membrane where phosphoinositide 3-kinase (PI3K) converts phosphatydlinositol 4, 5-diphosphate (PIP_2) to phosphatydlinositol 3, 4, 5-triphosphate (PIP_3).

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Acting as a downstream mediator of PI3K, Akt is phosphorylated on two key residues: serine 473 (S473) and threonine 308 (T308). Phosphorylation of T308 is performed by 3-phosphoinositide-dependent kinase 1 (PDK1) **(Fig. 1)**.

HER-2/neu proto-oncogene encodes a trans-membrane receptor tyrosine kinase. Once the HER-2/neu receptor istriggered, it activates the PI3K/Akt pathway. This cascade is triggered in cancer cells and related with the resistance of cancer cells to cisplatin and inhibition of PI3K/Akt increases its efficiency [1, 2, 3]. The most important event in cell survival mechanism by Akt is the altered function of pro-apoptotic proteins. Bad (a member of Bcl2 family) that is responsible for the down regulation of Bcl-xl and up regulates caspase 9, is phosphorylated at ser138 and consequently inhibited by Akt. Phosphorylation of Bax and pro-caspase 9 via Akt also results in the reduced apoptosis and increased resistance. Akt indirectly effects p53 by activating Mdm2 (murine double minute homologue 2) which in turns suppresses

p53. It has a direct effect on CDK (cyclin dependent kinase) inhibitor, p21 that act as downstream of p53 [4, 5, 6] **(Fig.1)**. Aktarbitrates cell survival and promotes chemo resistance by up regulation of Nf-kB. Aktencourages cell proliferation by activating mTOR (mammalian target of rapamycin) [7, 8, 9].

XIAP (X linked inhibitor of apoptosis) is a member of IAPs, a family of intracellular anti-apoptotic proteins and inhibits caspase3, caspase7 and caspase9. It acts like a substrate for Akt and after being phosphorylated by Akt its degradation is prevented proposing it to promote cell survival. So, inhibition of Akt, Nf-kB, XIAP and increased activation of PTEN, a negative regulator of AKT (phosphatase and tensin homolog deleted on chromosome 10) heightens the effects of cisplatin [10, 11, 12].

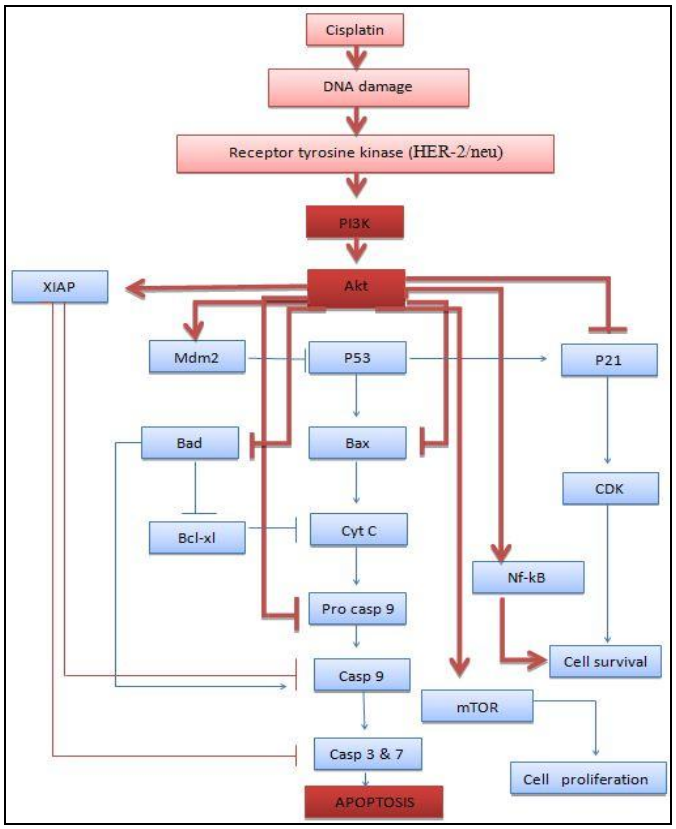

FIG.1: CISPLATIN AND PI3K/AKT PATHWAY.

This antagonizes the effect of cisplatin.

Cisplatin tempted MAPK signalling:

The participation of the MAPK pathway in cisplatin mechanism of action is dynamic. Mitogen-activated protein kinases (MAPKs) are a group of serine/threonine kinases which are activated by receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs) in response to a diverse range of extracellular spurs, which control cell growth, cell survival, differentiation and cell death. MAPK family consist of three main groups: extracellular signal-regulated kinases (ERK1/p44 and ERK2/p42) activated by growth factors and provides a protective effect against apoptosis, *c-jun*terminal kinase/stress-activated protein kinases (JNK/SAPK) and p38, which are stimulated and regulated by in response to stress such as DNA-damaging agents i.e., cisplatin and paclitaxel, hence plays an significant role in cell survival and apoptosis in cancer cells. Cisplatin activates MEK1 cascade and MAPKs and phosphorylation of these kinases is mainly through Ras (N-Ras, K-Ras, and H-Ras) and Rho (Rac 1, 2 and 3, Cdc42 and Rho A, B and C) families, Raf-1, A-Raf, B-raf, MAPK/ERK kinase 1–4 (MEKK1-4) [13, 14, 15] **(Fig. 2).**

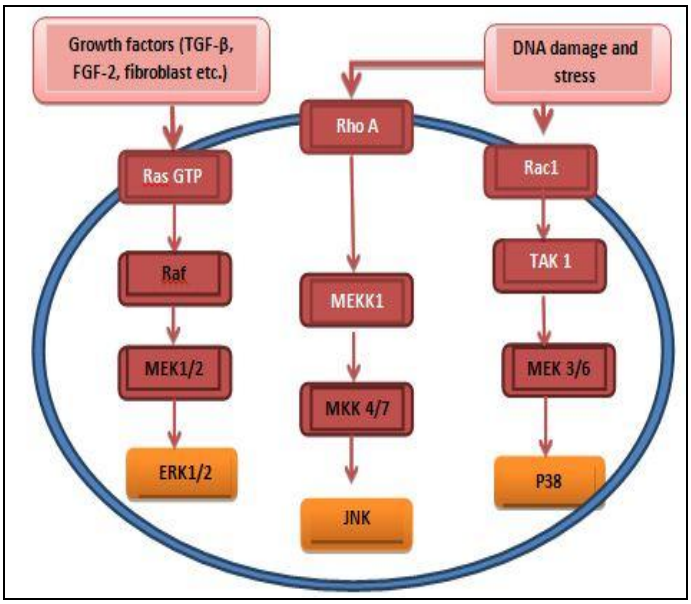

FIG. 2: ACTIVATION OF MAPK PATHWAY

a. JNK:

JNK, protein kinase playsanimperative role in the transcription of c-Jun, ATF-2, also activates FasL via transcription dependent apoptotic signaling. Cisplatin participates in the activation of JNK through the MAP/ERK kinase kinase (MEKK1) which then phosphorylates p53, activates caspase3 and initiates mitochondria-dependent apoptosis or it may enhance cell survival in cis-DDP treated cells.Any defect in JNK pathway; lack of MEKK1 effect, extended activation of stress kinases and phosphorylation of c-Jun and ATF-2 is coupled

with cisplatin resistance[16, 17]. JNK effectively regulates p53 by blocking its ubiquitination and degradation; hence it acts as Mdm2-independent regulator of p53 [18, 19].

In addition to JNK in p53 dependent apoptosis, it also induces p53 independent cell death by activating p73. JNK forms a complex with p73; any mutation in the binding site reduces the cisplatin sensitivity. cJUN prevents the proteosome mediated degradation of p73 and therefore, plays an important role against stress signals when p53 levels are truncated. However p73 mediated apoptosis is less efficient as compared to p53 and it requires the collaboration of other apoptosis regulators [20, 21, 22]. Activating transcription factor 3 is induced by stress or DNA damage and effects transcription through many apoptosis regulators. It can also be activated by many stress signaling pathways including BRCA1, p53 and MAPK (SAPK/c-JUN terminal kinase). Increased cisplatin cytotoxicity is associated with the increased ATF3 expression and vice versa [23, 24].

b. ERK:

Besides JNK and p53, cisplatin treatment also induces the tyrosine phosphorylation of ERK with the participation of Raf-1 and H-Rasonco-proteins. ERK activation is most crucial for cisplatin-tempted apoptosis and its inhibition leads to cisplatin resistance. Kinetics of cisplatin induced JNK and ERK activation is different and does not depends on each other [25, 26, 27].

ERK1/2 participates in cisplatin provoked mitochondrial decline, decrease in active Na^+ transport, and cell death. Cisplatin treatment initiates morphological dysfunction in mitochondria linked with cytochrome *c* release to the cytoplasm that acts as a major target for cisplatin in tumor cells. Cisplatin-resistant cells exhibit inhibition of cytochrome c release from mitochondria and decreased cell death as a consequence of overexpression of Bcl-xL. ERK indirectly causes the up-regulation of p21 and GADD45 and can roots cell cycle arrest. Phosphorylation and activation of Nf-kB has also shown pro-survival job of ERK[28, 29].Kinase suppressor of Ras1 (KSR1), a proto-onco gene, is an upstream activator of the ERK kinase. Low levels of*KSR1* gene or cells deficient in KSR1 are resistant to cisplatin cytotoxicity and show weak ERK instigation and apoptosis. On the other hand, reestablishment of KSR1in cancer cells, results in increased ERK activation and cis-DDP induced cytotoxicity. So, KSR1 mutations and over expression leads to the altered performance of cisplatin in cancerous cells [30, 31, 32].

c. p38 MAPK:

P38 MAPK is avital facilitator of cisplatin convinced cell death. Activation of p38 MAPK is linked with MKK3 and MKK6 and both are associated with the cisplatin cytotoxicity. p18, a p38 MAPK regulated protein is responsible to show the effects by interacting with p53 and stimulating the transcription of PUMA and NOXA to initiatecell death. In cis-DDP sensitive cells, activation of p38 MAPK and JNK is linked with the up-regulation of FasL and the reduced expression of FasL is correlated with the chemo-resistance[33, 34]. Another mediator of cisplatin induced cell death is apoptosis signal-regulating kinase 1 (ASK1), which is a member of the MAPKKK family that triggers both the SEK1-JNK and MKK3/MKK6-p38 signaling cascades **(Fig.3)**. ASK1/JNK/p38 activates Bax and exhibits a noteworthy role in pro-apoptotic function. On the other hand, Akt2 promotes resistance to cisplatin by inhibiting ASK1 and successively blocking p38 and JNK activity [35, 36, 37].

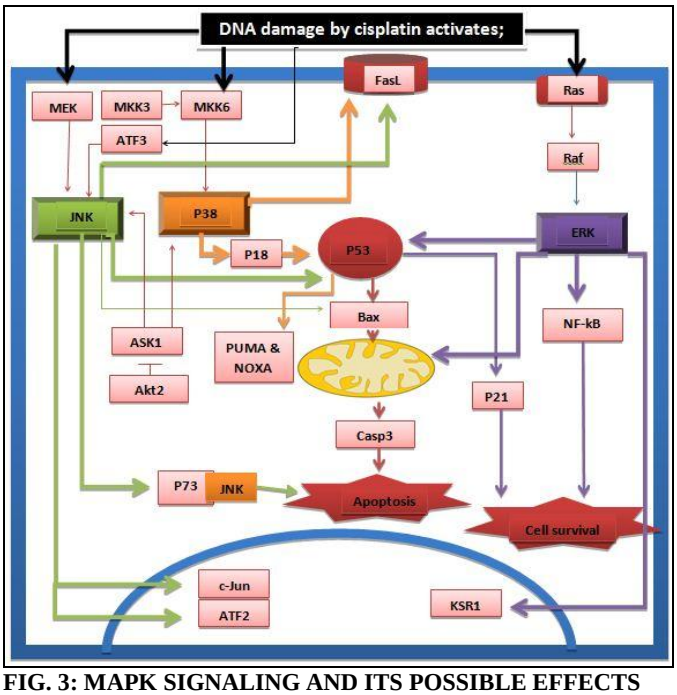

FIG. 3: MAPK SIGNALING AND ITS POSSIBLE EFFECTS

Role of extrinsic death receptor pathways:

Fas/FasLigand and its promising role:

As mentioned earlier, programmed cell death is performed by the action of a family of cysteine-dependent aspartate-directed proteases (caspases) that includes initiator caspase 8 & 9 and effector caspase 3, 6 &7. Extrinsic pathway of apoptosis is associated with the action of FasL, TRAIL, and TNF- α and their receptors Fas, TRAIL receptor, TNF-RI respectively. Cisplatin considerably increases the activity of these apoptosis inducing death receptor pathways.

Fas/FasL is another important signaling pathway which is initiated by number of stimuli, most importantly by DNA damage by cisplatin. In addition, it is also activated as a downstream of many stress signaling pathways including p53 and MAPK. The mitochondria independent apoptosis is mediated through Fas/FasL and plays amomentous role in chemotherapy by increasing cisplatin encouraged cytotoxicity in many tumor cells. However, many tumor cells can inactivate Fas/FasL in response to cisplatin and confers to resistance. Fas receptor is an integral membrane protein which belongs to tumor necrosis factor super family, whereas Fas ligand is transmembrane protein.

Activation process includes the binding of Fas ligand with Fas receptor at adaptor molecule Fas-associated death domain that induces its trimerization and ensuing in the formation of DISC (death-inducing signaling complex). This complex then directly binds to caspase 8, leading to activation of caspase 8. DISC plus caspase 8 then activate caspase 3, which is the main initiator of apoptosis. Inability of cisplatin in provoking Fas/FasL response or the failure of activation of this pathway by MAPK is responsible for the chemoresistance and underlies the prominence of Fas/FasL. In addition, association of caspase 8 and BH3-only protein Bid links both intrinsic and extrinsic apoptosis pathways. It cleaves the Bid (tBid) which then translocates in mitochondria and releases cytochrome c resultingin apoptosis [38-42].

TRAIL:

Another important death receptor is TRAIL (tumor-necrosis factor-related apoptosis-inducing ligand) which belongs to tumor necrosis family and act as a potent inducer of apoptosis without damaging the normal cells. It has been shown that TRAIL induces apoptosis in some of cancer cells by binding to its cell surface receptor (death receptor 4and 5). Cytoplasmic death domain is required for TRAIL receptor-induced apoptosis on DR4 and DR5 both which then mediates the formation of DISC by recruiting FADD and caspase 8, thus leads to the initiation of apoptosis with the aid of caspase 3 and 7. FADD-like interleukin-1β-converting enzyme-inhibitory protein (c-FLIP) is the inhibitory regulator of TRAIL and Fas/FasL which interacts with FADD and caspase 8 and suppresses the cytotoxic effects of cisplatin [43, 44, 45]. Studies have shown that cisplatin up regulates DR5 and induces the cleavage of c-FLIP by the activation of caspase 3**(Fig. 4)**.

Consequently, caspase 8 releases and TRAIL activity is restored in cancer resistant cells[46, 47]. Cisplatin induced cytotoxicity at the level of TRAIL and Fas can be regulated by increasing the expression of death receptors and pro-apoptotic proteins, formation of DISC complex, increasing the cleavage of FLIP, and by stabilizing mitochondrial depolarization.

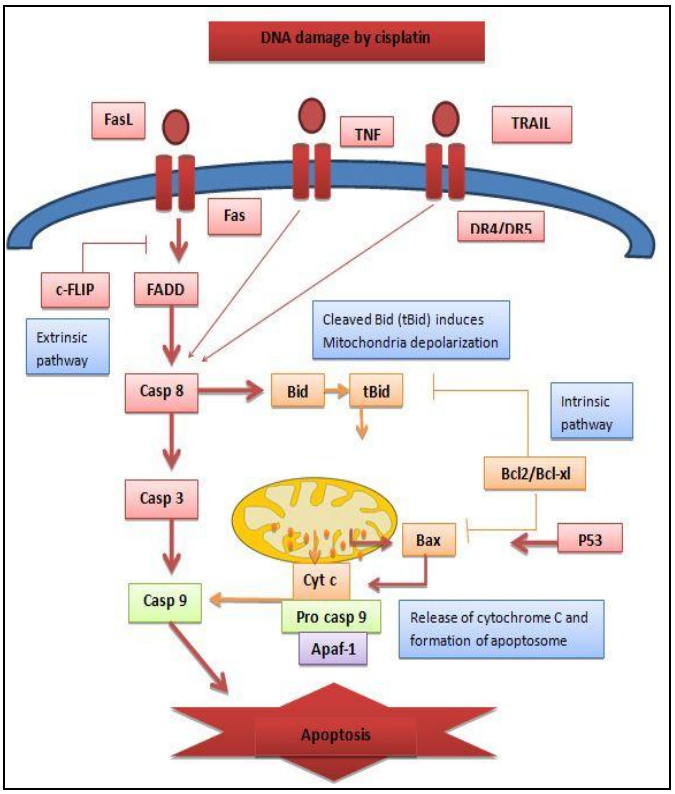

FIG. 4: DEATH RECEPTOR PATHWAY

Adverse effect of TNF alpha activation:

TNF alpha is an important pro-inflammatory cytokine which is generally activated by macrophages and exerts its inflammatory effects and induce apoptosis. Studies have shown that it is also activated by cisplatin in kidney cells hence proving itself as a main cause of nephrotoxicity after cisplatin treatment **(Fig. 5)**. Its transcription is regulated by NF-kB and c-AMP response element etc. However, cisplatin indirectly activates NF-kB by the action of Akt, which then increases the expression of TNF alpha-mRNA. Furthermore, TNF alpha-mRNA translation is highly dependent upon p38 MAPK which is again being activated by cisplatin. So, cisplatin contributes in both the formation of TNF alpha mRNA and its p38 MAPK dependent translation which demonstrate its role in inducing renal injury during cisplatin chemotherapy [48, 49].

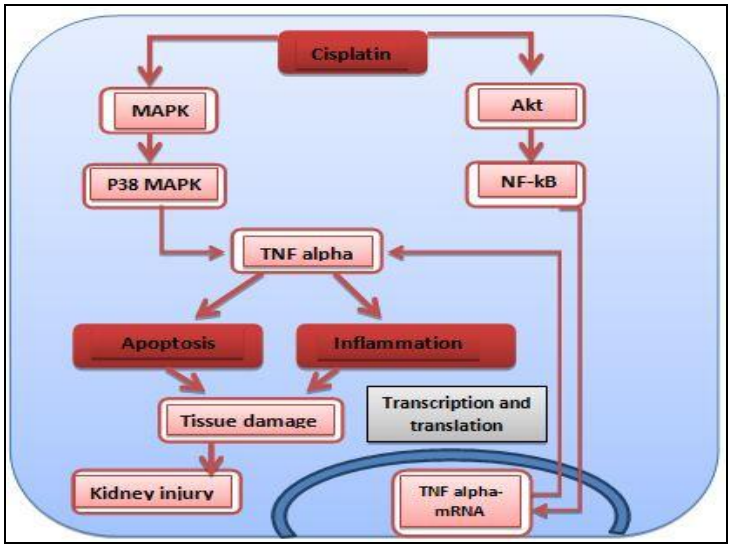

FIG. 5: CISPLATIN INDUCED NEPHROTOXICITY

Cisplatin Resistance:

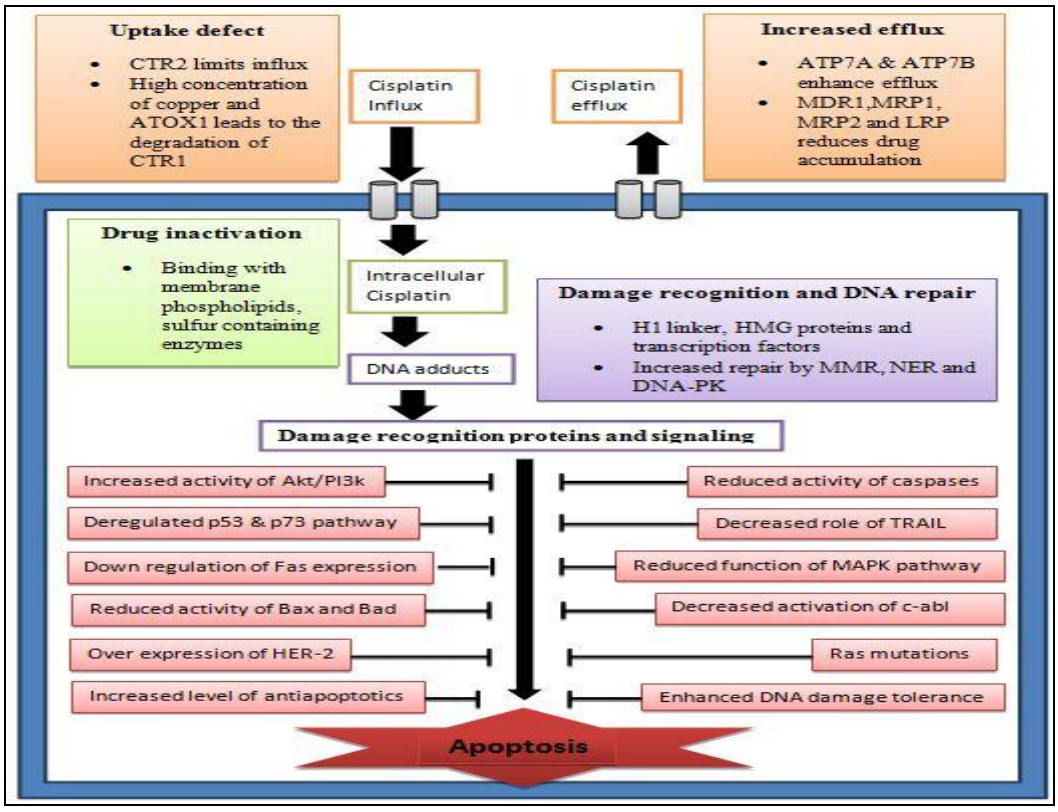

FIG. 6: CHEMORESISTANCE AND SUPPRESSED EFFECT OF CISPLATIN

CONCLUSION AND PERSPECTIVES: In future, it is better to deliberate on adjuvant/combination therapy of cisplatin that can evade the drug resistance by upsetting the mode of action of the drug instead of manufacturing the novel drugs that may target the precise pathway. Afascinating strategy would be the transfer of gene or a molecule as an activator or inhibitor that intermingles with signaling processes, addition of a molecular fragment along with platinum complex that can interfere with the specific pathway would expand the efficacy of therapeutic responses of platinum compounds.

All the familiarity about biochemical mechanism of cisplatin brought DNA damage leads to the development of amended platinum complexes bound with different moieties or functional groups that may act as either Akt, RB, TNF alpha and MAPK inhibitor or stimulator of c-Abl, Fas, TRAIL and p53 or transfer of specific receptor for the attached molecules would strikingly lift up the worth of platinum compounds.

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