

Review Article

The role of Aurora-A in human cancers and future therapeutics

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Abstract: Aurora-A is a mitotic serine/threonine-protein kinase and an oncogene. In normal cells, Aurora-A appears from G2 phase and localizes at the centrosome, where it participates in centrosome replication, isolation and maturation. Aurora-A also maintains Golgi apparatus structure and spindle assembly. Aurora-A undergoes ubiquitination-mediated degradation after the cell division phase. Aurora-A is abnormally expressed in tumor cells and promotes cell proliferation by regulating mitotic substrates, such as PP1, PLK1, TPX2, and LAST2, and affects other molecules through a non-mitotic pathway to promote cell invasion and metastasis. Some molecules in tumor cells also indirectly act on Aurora-A to regulate tumor cells. Aurora-A also mediates resistance to chemotherapy and radiotherapy and is involved in tumor immunotherapy. Clinical trials of Aurora-A molecular inhibitors are currently underway, and clinical transformation is just around the corner.

Keywords: Aurora-A, cancer, clinical

Introduction

The Aurora kinase family is a class of serine/threonine protein kinases that was first discovered by Chan et al. in 1993 and named lpl1 [1]. In 1995, Glover discovered a gene homologous to lpl1 and named it Aurora-A (also known as aurka, STK6/BTAK) [2]. The Aurora gene family in humans includes Aurora-A, Aurora-B, and Aurora-C [3]. Aurora-A has been the subject of intense investigation because of its powerful regulatory roles on a variety of signaling pathways. The human Aurora-A gene is located on chromosome 20q13 [4, 5], and the structure of Aurora-A is shown in **Figure 1**. The N-terminal contains a localization domain that localizes Aurora-A on the centrosome in a microtubule-dependent manner. The C-terminal, a catalytic domain, contains two conserved domains: an activation loop and a degradation box (D-Box) [6, 7]. The activation loop comprises a highly conserved RxT motif, and phosphorylation of the motif at the threonine induces activation of Aurora-A [8]. The D-Box mediates degradation

of Aurora-A through the ubiquitin-mediated proteasome pathway [9, 10].

Aurora-A was first discovered as a mitotic kinase that phosphorylates specific substrates and participates in centrosome and spindle activity during mitosis [11]. As studies on tumor development increased, Aurora-A was later found to be an oncogene that shows gene amplification and overexpression in a variety of human tumors [12, 13]. Aurora-A is used not only as a target for cancer treatment but also has such uses as a molecular marker for cancer diagnosis and prognosis, and for influencing cell proliferation, migration and metastasis [14-20]. In this review, we discuss the role of Aurora-A in mitosis and the regulatory mechanisms of Aurora-A in tumor cells. We also summarize the current clinical trials and results from Aurora-A inhibitors.

Biological function

The expression of Aurora-A is dependent on the cell cycle. Aurora-A is expressed at low levels in

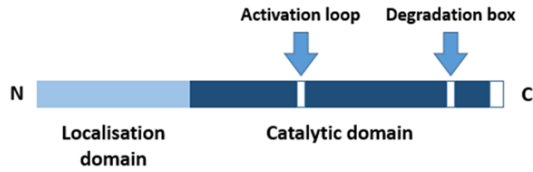


Figure 1. Aurora-A structure diagram.

the G1 and S phases and peaks at the G2 and M phases. Aurora-A is then ubiquitinated and degraded after the cell division phase [8, 21]. Aurora-A is activated during the G2 to M phase transition, when it is mainly responsible for the maturation and separation of centrosomes, assembly of bipolar spindles, and regulation of mitotic processes (**Figure 2**).

Aurora-A localizes on the centrosome in G2 and M phases, a process that is regulated by the Golgi apparatus [22-24]. The Golgi apparatus raises Aurora-A to target centrosomes in G2 phase, which is crucial to promoting the maturity of centrosomes [25]. Aurora-A simultaneously regulates Golgi structure stability after mitosis [26]. The centrosome replicates into two undivided centrosomes before the late S phase, but this process does not seem to involve Aurora-A, which only appears in the G2 phase. However, *in vitro* experiments have shown that Aurora-A overexpression causes centrosome amplification [27, 28]. Therefore, we speculate that Aurora-A may be indirectly involved in centrosome replication in some way. The copied centrosome must be separated to form a bipolar spindle, which requires the participation of Aurora-A. Inhibition of Aurora-A results in the formation of a unipolar spindle containing two unseparated centrosomes [2, 22, 29]. For mitosis to continue, the isolated centrosome needs to recruit various proteins, such as γ -tubulin and centrosome proteins, which also requires Aurora-A [30]. During this process, Aurora-A also assists the spindle assembly checkpoint (SAC) to check the accuracy of the chromosomal centromere connection with microtubules [31]. The main role of Aurora-A after the spindle is formed is to stabilize the structure of the spindle [32]. Inhibiting Aurora-A not only renders the spindle structure unstable, but also reduces the star-shaped microtubules and spindle length [33-35].

Regulatory mechanisms in tumors

Tumorigenesis and development

Aurora-A exhibits a dual role in tumor cells. Aurora-A regulates molecules and substrates during mitosis, and it influences molecules and signals involved in tumor biological processes, such as proliferation, migration, invasion, metastasis, tumorigenesis, and apoptosis [36-40]. Aurora-A regulates multiple molecules and signaling pathways, such as p53/p73, p27, PP1, BRCA, Ras, the MEK/ERK signaling pathway, PLK1, TPX2, the NF- κ B signaling pathway, the Hippo signaling pathway, the PI3K/Akt/mTOR signaling pathway, RIPK1/3, MLKL, the Wnt/ β -catenin pathway, and the p38 MAPK signaling pathway, among other factors. Aurora-A is also regulated by several cellular microRNAs and long non-coding RNAs (lncRNAs) [41-43] (**Figure 3**).

p53/p73

p53, a pro-apoptotic factor, is phosphorylated by Aurora-A at Ser 315, which facilitates MDM2-mediated ubiquitination of p53 [44], and at Ser 215, which inhibits transcriptional activity of p53 [45]. In HCT116 cells, multiple myeloma SET domain proteins (MMSET), an epigenetically modified molecule, methylates Aurora-A to promote ubiquitination of p53 and reduction of p53 stability [46]. In response to decreased p53 levels, apoptosis is reduced, indicating a potential anti-cancer activity of p53. p73, a member of the p53 family, shows a similar structure and biological activity to p53 and also acts as a pro-apoptotic protein [47]. In p53-deficient hepatocellular carcinoma cells, inhibition of Aurora-A activates p73-mediated apoptosis, and p73 is regarded as a new target for p53-deficient cancer cells [48, 49].

p27

p27 (Cyclin-dependent kinase inhibitor 1B) serves as a regulator of cell proliferation as well as a tumor suppressor relying on varying post-translational modifications [50]. In gastric cancer, Aurora-A promotes p27 to reduce c-Bax-mediated apoptosis. Bcl-2 binds to Bax to inhibit Bax-mediated apoptosis. In gastric cancer, p27 inhibits the cleavage of Bax, a mitochondrial apoptosis activator, which leads to increased apoptosis and disruption of suppres-

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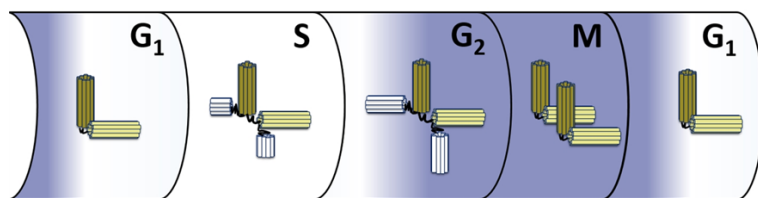


Figure 2. Schematic diagram of changes in centromere and Aurora-A during the cell cycle. The background color in the figure represents the expression level of Aurora-A.

sion by Bcl-2. Overexpressed Aurora-A downregulates calpain, which represses p27 and mediates Bax cleavage [51].

PP1

Aurora-A interacts with protein phosphatase 1 (PP1) in a balanced feedback regulation mechanism that is required for cell cycle progression of normal cells. PP1 binding to Aurora-A is essential for Aurora-A activation. Activated Aurora-A then phosphorylates PP1 to repress PP1, and in turn, PP1 inhibits Aurora-A by dephosphorylating certain sites in Aurora-A [52]. When this balance is disrupted, cells tend to undergo malignant changes. Phosphatase 1 nuclear targeting subunit (PNUTS), a protein that is crucial for mitotic stability and that is overexpressed in cancer cells, is involved in the process by which PP1 dephosphorylates Aurora-A in mammalian cells [53]. Thus, the ratio of Aurora-A to PP1 may be a prospective biomarker to predict tumorigenesis and allow for early diagnosis.

BRCA1/2

Oxidative stress induces single strand DNA single-strain break (SSB) in normal cells, which requires poly ADP-ribose polymerase (PARP) intervention for repair. If PARP is inhibited during this process, the SSBs leads to double-strain breaks (DSB), which requires BRCA for repair. In the absence of BRCA, these types of DNA damage lead to cell aberrations and subsequent tumorigenesis [54]. In normal cells, BRCA1 is phosphorylated and restrained by Aurora-A, while it is positively regulated by PP1 [55]. In ovarian carcinoma, overexpressed Aurora-A regulates DNA repair through its negative effects on BRCA1/2 [56, 57].

Ras

The oncogene Ras, which contains three mutations, K-Ras, H-Ras, and N-Ras, promotes genomic instability through a positive effect on Aurora-A [58]. In ovarian cancer, Ras promotes Aurora-A expression and downregulates BRCA2, resulting in an imbalance in the ratio of Aurora-A to

BRCA2, leading to chromosomal instability and tumorigenesis [59]. KRAS exhibits similar biological activity as RAS and has a positive effect on Aurora-A in lung cancer [60]. In gastrointestinal cancer, KRAS promotes the expression of Aurora-A and subsequent Aurora-A-mediated phosphorylation of ribosomal protein S6 kinase B1 (RPS6KB1, mitosis-related protein) at T389, thereby promoting cell proliferation [61]. In breast cancer, Ras downstream signaling pathways such as the Ras-MAPK signaling pathway also participate in the regulation of Aurora-A [62].

MEK/ERK signaling pathway

The MEK/ERK signaling pathway is a Ras-MAPK signaling pathway that is activated by Aurora-A and Ras in triple-negative breast cancer, bladder cancer, and melanoma. In turn, ERK reacts to Aurora-A, promoting ERK and Aurora-A [63-65].

PLK1

Polo-like kinase 1 (PLK1) is a powerful cell cycle regulator that is activated in G2 phase under the combined action of Aurora-A and its cofactor Bora (protein aurora borealis) and functions in the M phase. PLK1 is phosphorylated by Aurora-A at Thr 210 and regulates centrosome maturation, spindle assembly, and chromosome segregation [66, 67]. Both Aurora-A and PLK1 have been identified as potential targets in chondrosarcoma [68]. In HeLa cells and nasopharyngeal carcinoma cells, the combined use of inhibitors against Aurora-A and PLK1 results in mitotic catastrophe [69]. In breast cancer, activated PLK1 motivates cell division cycle 25 (CDC25) to promote the cell cycle-related CCND1-CDK4/6 axis and proliferation. However, BRCA1 disturbs the interaction bet-

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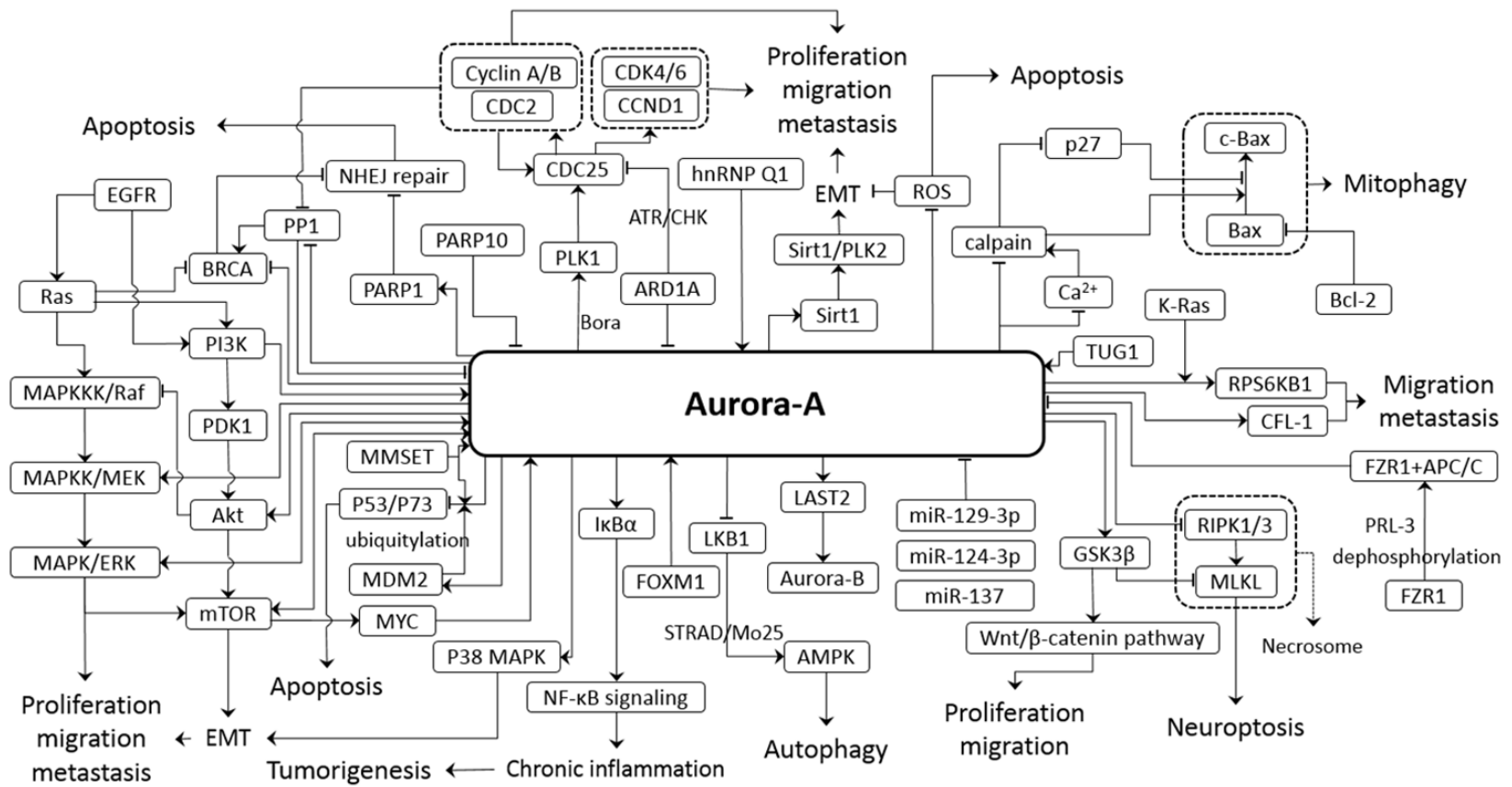


Figure 3. Regulation of tumorigenesis and development.

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ween Aurora-A and Bora to repress PLK1 [70]. Therefore, molecules that activate BRCA1 may represent new opportunities for the treatment of breast cancer.

TPX2

Targeting protein for XKLP2 (TPX2) is a substrate of Aurora-A and is highly expressed in cancer cells. TPX2 helps Aurora-A localization to the spindle, while Aurora-A phosphorylates TPX2 to regulate the process of the spindle [71, 72]. TPX2 deficiency causes genomic instability and apoptosis [73].

NF- κ B signaling pathway

In gastric cancer, Aurora-A phosphorylates I κ B α , a key molecule in the NF- κ B signaling pathway, to activate the NF- κ B signaling pathway. Activation of NF- κ B causes chronic inflammation of the stomach, resulting in tumorigenesis [74].

Hippo signaling pathway

Large tumor suppressor 1/2 (LAST1/2) are kinases in the Hippo signaling pathway that act as tumor suppressors [75, 76]. In normal cells, LAST2 is phosphorylated by Aurora-A at Ser 380 during mitosis to activate Aurora-B, promising well-balanced cell cycle, which makes no difference with LAST2 to serve in Hippo signaling pathway [77]. Both Aurora-A and LATS2 are overexpressed in chronic myeloid leukemia [78]. Therefore, we speculate that the Aurora-A-LAST2-Aurora-B axis may be important in chronic myeloid leukemia or other solid tumors.

PI3K/Akt/mTOR signaling pathway

The PI3K/Akt/mTOR signaling pathway and Aurora-A have a mutual feedback regulation effect in human epithelial ovarian cancer, glioblastoma, prostate cancer, and breast cancer [79-83]. In lung cancer, both the EGF/EGFR signaling pathway and Aurora-A overexpression activate the PI3K/Akt/mTOR signaling pathway [84]. In neuroblastoma, PI3K and mTOR act on Aurora-A to promote Aurora-A expression directly and regulate its transcription level by promoting MYC indirectly, which is activated to promote epithelial-mesenchymal transition (EMT), thereby promoting tumor proliferation, migra-

tion, metastasis, and invasion and inhibiting apoptosis [85]. In human glioblastoma multi-form stem cells, phosphoinositide-dependent kinase-1 (PDK1) serves as a link between PI3K and Akt [86].

RIPK1/3 and MLKL

Necroptosis, a form of apoptosis, involves receptor-interacting serine/threonine kinase 1 (RIPK1), receptor-interacting serine/threonine kinase 3 (RIPK3), and mixed lineage kinase domain-like (MLKL), which are all necrosome components. During necroptosis, the RIPK1-RIPK3 complex activates MLKL to mediate the final lethal step [87, 88]. In pancreatic carcinoma, Aurora-A represses both the RIPK1-RIPK3 complex and MLKL, thus inhibiting necroptosis. Aurora-A binds the RIPK1-RIPK3 complex to inhibit it. Aurora-A suppresses the RIPK3-MLKL complex via phosphorylating glycogen synthase kinase 3 β (GSK3 β) at Ser 9 [89].

Wnt/ β -catenin pathway

Wnt/ β -catenin pathway is closely related to Aurora-A. In colorectal cancer, the Wnt/ β -catenin pathway is downregulated by Aurora-A, although the mechanisms have not been identified and require further exploration [90]. Active GSK3 β phosphorylates β -catenin, leading to β -catenin degradation [91]. As mentioned above, in pancreatic carcinoma, Aurora-A phosphorylates GSK3 β at Ser 9 to restrain GSK3 β [89]. We thus speculate that inactive GSK3 β issue in β -catenin accumulation mediates Wnt/ β -catenin pathway activation.

p38 MAPK signaling pathway

p38 MAPK is a member of the MAPK family of proteins. p38 MAPK is activated by Aurora-A and plays a role in promoting tumor EMT in melanoma and glioblastoma. Aurora-A inhibitors inhibit p38 MAPK activation, mediating apoptosis and autophagy. p38 MAPK is speculated to function in apoptosis and autophagy [83, 92].

MicroRNAs and lncRNA

Several microRNAs and long non-coding RNAs (lncRNA) that play vital regulatory roles in cells have also been shown to regulate Aurora-A. For example, some microRNAs, which are down-regulated in cancer cells, also limit Aurora-A

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expression: methylation-mediated downregulated miR-129-3p which promotes EMT, invasion and metastasis in hepatocellular cancer; miR-124-3p, which affects proliferation, migration and apoptosis in bladder cancer [93]; and miR-137, which is involved in chromosomal instability in multiple myeloma [94]. In adult acute myeloid leukemia and epithelial ovarian cancer, the lncRNA taurine-upregulated gene 1 (TUG1) promotes proliferation via inducing Aurora-A expression [95, 96].

PARP

The PARP family is a group of ribozymes that contains 18 members. Both PARP1 and PARP10 have been shown to functionally interact with Aurora-A in cancer cells. In ovarian cancer, Aurora-A inhibition decreases PARP1, which mainly participates in DNA repair, leading to the more error-prone non-homologous end-joining (NHEJ) repair and eventually resulting in apoptosis [56]. In hepatocellular carcinoma, PARP10, which functions differently than PARP1, mono-ADP-ribosylates and inactivates Aurora-A, leading to reduced migration, invasion, and metastasis [97].

CDC25

The cell cycle regulator CDC25 is regulated by Aurora-A and AT-rich interactive domain 1A (ARID1A), a tumor suppressor that is mutated in many tumors. In colorectal cancer, ARID1A indirectly inhibits CDC25 and PLK1 by decreasing Aurora-A expression and directly inhibits CDC25 through the ARID1A/ATR/CHK pathway, thereby inhibiting the cell cycle and regulating cell proliferation [98]. In breast cancer, Aurora-A regulates CDC25 to promote cancer progression [70].

Sirtuin 1 (Sirt1)

Sirt1 is a key protein involved in centromeric replication. The interaction between Sirt1 and PLK2 facilitates the cell cycle and EMT [99]. In human epithelial ovarian cancer cells, the Aurora-A inhibitor induces cell apoptosis and autophagy, possibly through restraining Sirt1 expression. The specific regulatory mechanism needs further study [79].

LKB1

In non-small cell lung cancer (NSCLC), liver kinase B1 (LKB1, or STK11) interacts with

STARD and Mo25 to catalyze the phosphorylation of AMPK to facilitate autophagy. Aurora-A phosphorylates and inactivates LKB1, preventing it from binding STARD and Mo25 to promote tumor cell development [100].

Other functions and pathways

In oral squamous cell carcinoma, inhibition of Aurora-A promotes reactive oxygen species (ROS) production and tumor apoptosis [101]. In colorectal cancer, hnRNP Q1 influences cell proliferation and tumorigenesis by controlling Aurora-A translation [102]. In papillary thyroid cancer, cofilin-1 (CFL-1), an actin-binding protein, is dephosphorylated by Aurora-A to catalyze its activation and tumor migration [103]. In colorectal cancer, fizzy and cell division cycle 20 related 1 (FZR1) is dephosphorylated by phosphatase of regenerating liver-3 (PRL-3) and interacts with the anaphase-promoting complex/cyclosome (APC/C) complex to promote Aurora-A ubiquitination [104].

Two spindle formation modes exist in mammalian cells: centrosome-dependent and non-centrosome-dependent mitosis. In NSCLC cells, Aurora-A plays a role in both processes. Inhibition of the centrosome-dependent protein SMARCA4 increases Aurora-A regulation of spindle formation and NSCLC cell sensitivity to Aurora-A inhibitors [105].

Aurora-A may localize in mitochondria in tumor cells to promote mitochondrial fusion, thereby generating more ATP and providing more energy support for tumor cells, which is beneficial to tumor cell proliferation [106].

Chemoresistance and radioresistance

In addition to directly regulating the occurrence and development of tumors, Aurora-A also exerts a negative influence on the efficacy of chemotherapy and radiotherapy, based in part on its increased expression in resistant tumor cells (**Figure 4**). Aurora-A overexpression induces radiotherapy resistance in many cancers such as lung cancer, hepatocellular carcinoma, cervical squamous cell carcinoma, glioblastoma, nasopharyngeal carcinoma, and prostate cancer [107-109]. In breast cancer, pancreatic cancer, and ovarian epithelial cancer, Aurora-A overexpression increases the chemoresistance and radioresistance of tumor cells by upregulating the ATM/Chk2-mediated DNA damage

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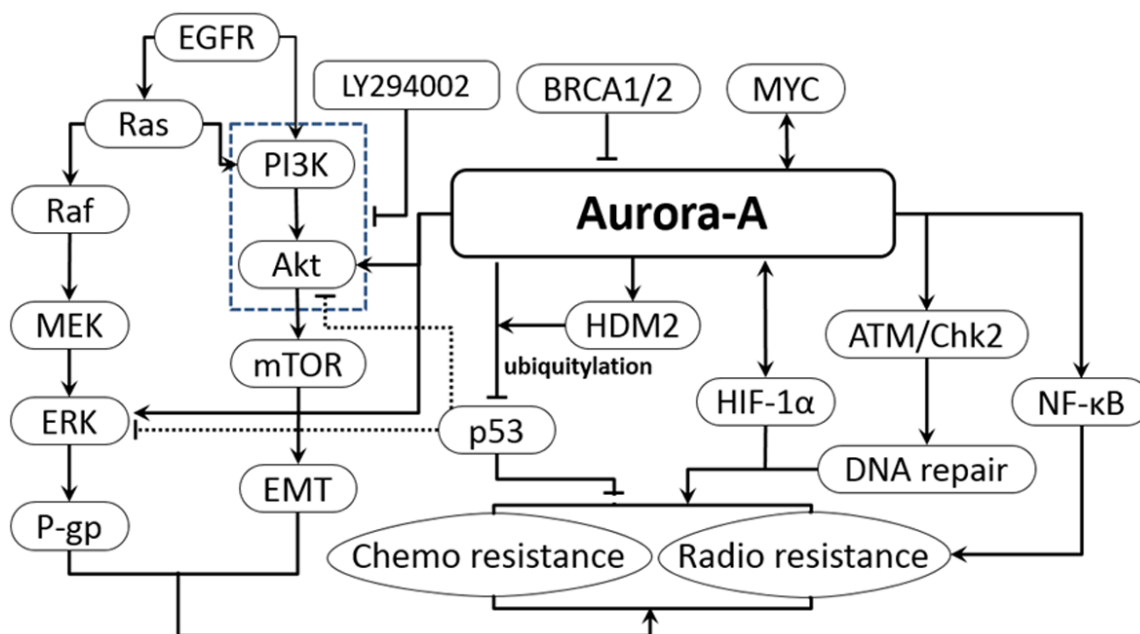


Figure 4. Mechanism of Aurora-A mediated chemotherapy and radiotherapy.

repair network, which can be inhibited by BRCA1/2 [110]. Clinical data suggest that elevated Aurora-A expression in NSCLC, ovarian cancer, and oral squamous cell carcinoma is related to cisplatin resistance [111-114]. In endometrial cancer, Aurora-A increases cisplatin and PTX resistance by sensitizing AKT/mTOR signaling pathway [115]. Aurora-A promotes ERK phosphorylation and regulates P-gp (a multidrug resistance transporter that takes Taxol as substrate), which ultimately leads to Taxol resistance in breast cancer [116]. In triple-negative breast cancer, FOXM1 is stabilized by Aurora-A to promote PTX resistance [117]. Aurora-A and MYC interact with each other in Myc-overexpressing lymphoma to mediate cancer cell resistance to cyclophosphamide. Inhibition of Aurora-A overexpression reduces the chemotherapy resistance of lymphoma while suppressing MYC overexpression [118]. Aurora-A causes laryngeal squamous cell carcinoma cells to hibernate in the manner of the activation ERK1/2 pathway [119]. High expression of Aurora-A enables cancer stem cells in colorectal cancer to develop resistance to 5-FU [120]. In lung cancer, EGFR-TKI resistance is related to the interaction between Aurora-A, Ras, and p53 [121, 122]. Imatinib resistance in chronic myelogenous leukemia cells is also closely related to Aurora-A overexpression in tumor cells, although the related signaling is unknown [123]. In nasopharyngeal

carcinoma, Aurora-A works synergistically with HIF-1α to promote the radiotherapy and chemotherapy resistance of cancer cells [124]. In lung cancer cells, Aurora-A may affect radiotherapy sensitivity by upregulating NF-κB expression and downregulating p53 expression [125, 126]. NF-κB also functions in the radioresistance of hepatocellular carcinoma regulated by Aurora-A [127]. Intriguingly, radiation also promotes HCC metastasis by activating Aurora-A to promote tumor stem cell proliferation through the PI3K/Akt signaling pathway [128].

Immunotherapy

Tumor immunotherapy mobilizes the host immune system and enhances the ability of anti-tumor immunity in the tumor microenvironment to control and kill tumor cells [129]. Aurora-A is considered an antigen target for immunotherapeutic attacks [130-132]. In breast cancer, suppression of Aurora-A greatly changes the immunogenic microenvironment of tumor cells, which is conducive to the enrichment of cytotoxic T cells (CTLs). Also, the suppression of Aurora-A is harmful to immunosuppressive myeloid-derived suppressor cells (MDSCs) in which apoptosis is induced by reduced ROS production through the Stat3 pathway [133]. In peripheral T-cell lymphoma, the simultaneous application of PD-L1 and Aurora-A inhibitors

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Table 1. Aurora kinase inhibitors

Inhibitor	Molecular Formula	Target	Current status	DLT	AE	Condition	Reference
PHA-79358 (Danusertib)	$C_{26}H_{30}N_6O_3$	Aurora-A (IC50: 13 nmol/L) Aurora-B (IC50: 79 nmol/L) Aurora-C (IC50: 61 nmol/L)	Phase 2	-Bullous dermatitis -Febrile neutropenia -Mucositis -Syncope	-Anorexia -Constipation -Diarrhea -Fatigue -Nausea -Progressive Pneumonia -Thrombocytopenia	-Advanced Solid Tumors -Breast, Ovarian, Colorectal, Pancreatic Cancer, SCLC, NSCLC -CML -Metastatic hormone refractory Prostate Cancer -Metastatic castration-resistant prostate cancer after docetaxel failure -Multiple Myeloma	[182-187]
MK-0457 (VX-680, Tozasertib)	$C_{23}H_{28}N_8OS$	Aurora-A (Ki: 0.6 nM) Aurora-B (Ki: 18 nM) Aurora-C (Ki: 4.6 nM)	Phase 2	-Herpes zoster -Neutropenia	-Alopecia -Diarrhea -Fatigue -Nausea -Transient mucositis -Vomiting	-Advanced Solid Tumors -BCR-ABL T315I mutant CML, Philadelphia chromosome-positive ALL -Colorectal Cancer	[188-190]
MSC1992371A	$C_{24}H_{30}FN_7O$	Aurora-A Aurora-B Aurora-C	Phase 1	-Diarrhea -(Febrile or not) Neutropenia -Mucositis/stomatitis -Sepsis	-Anemia -Fatigue -Thrombocytopenia	-Advanced Hematologic Malignancies -Solid Tumors	[191, 192]
ABT-348 (Iloraser-tib)	$C_{25}H_{21}FN_6O_2S$	Aurora kinase VEGFR	Phase 2	-Hypertension -Pancreatitis	-Anemia -Hypokalemia -Hypophosphatemia	-Advanced Solid Tumors -ALL, AML, B-cell CLL, CML, Myelodysplasia -Hematologic Malignancies -Metastatic Malignant Neoplasm, Solid Neoplasm, Unresectable Malignant Neoplasm	[193]
BI-847325	$C_{29}H_{28}N_4O_2$	Aurora kinase MEK	Phase 1	Reversible hematologic and gastrointestinal toxicities	-Anemia -Diarrhea -Decreased appetite -Fatigue -Nausea -Neutropenia -Vomiting	-Advanced Solid Tumors	[194]
ENMD-2076	$C_{21}H_{25}N_7$	Aurora kinase VEGFR	Phase 2	-Fatigue -Hypertension -Neutropenia -Syncope -Typhlitis -QTc prolongation	-Diarrhea -Fatigue -Nausea -Vomiting	-Advanced Solid Tumors -Advanced, Metastatic, Soft Tissue Sarcoma -Advanced Adult Hepatocellular Carcinoma, Advanced Fibrolamellar Carcinoma -Metastatic Triple-Negative Breast Cancer -Multiple Myeloma -Relapsed or Refractory Hematological Malignancies -Ovarian Clear Cell Carcinoma -Ovarian Cancer, Fallopian Cancer, Peritoneal Cancer	[195-198]

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AT9283	$C_{19}H_{23}N_7O_2$	Aurora-A Aurora-B	Phase 2	<ul style="list-style-type: none"> -Cardiomyopathy -(Febrile or not) Neutropenia -Hypertension -Infection -Myocardial infarction -Multiorgan failure -Pneumonia -Tumor lysis syndrome 	<ul style="list-style-type: none"> -Alopecia -Anemia -Fatigue -Gastrointestinal disturbance -Lymphocytopenia -Myelosuppression -Mucositis -Thrombocytopenia -Vomiting 	<ul style="list-style-type: none"> -Advanced Solid Malignancies -Multiple Myeloma -Non-Hodgkins Lymphoma, Unspecified Adult Solid Tumor -AML, ALL, CML, Myelodysplastic Syndromes, Myelofibrosis -Unspecified Childhood Solid Tumor 	[199-204]
AMG900	$C_{28}H_{21}N_7OS$	Aurora-A Aurora-B	Phase 1	<ul style="list-style-type: none"> -Abnormal pain -Increases in alanine aminotransferase and aspartate aminotransferase -Neutropenia -Pancytopenia -Thrombocytopenia 	<ul style="list-style-type: none"> -Anemia -Diarrhea -Fatigue -Leukopenia -Nausea 	<ul style="list-style-type: none"> -Advanced Adult Solid Tumors -AML -Hematologic Malignancies 	[205, 206]
PF-03814735	$C_{23}H_{25}F_3N_6O_2$	Aurora-A Aurora-B	Phase 1	<ul style="list-style-type: none"> -Febrile neutropenia -Increase of aspartate aminotransferase -Left ventricular dysfunction 	<ul style="list-style-type: none"> -Anemia -Diarrhea -Decreased appetite -Fatigue -Nausea -Vomiting 	<ul style="list-style-type: none"> -Advanced Solid Tumors 	[207]
MLN8237 (Alisertib)	$C_{27}H_{20}ClFN_4O_4$	Aurora-A	Phase 3	<ul style="list-style-type: none"> -Abdominal pain -Asthenia -Anorexia -Bullous dermatitis -Fatigue -(Febrile or not) Neutropenia -Headache -Leukopenia -Liver transaminases elevation -Mood alteration/depression -Nausea -Oropharyngeal mucositis -Oral pain -Somnolence -Stomatitis -Thrombocytopenia -Urinary tract infection 	<ul style="list-style-type: none"> -Anemia -CNS toxicities -Cytopenia -Diarrhea -Dysgeusia -Hypocalcemia -Lymphopenia -Memory impairment -Neuropathy -Thrombocytopenia -Vomiting 	<ul style="list-style-type: none"> -Advanced Solid Tumors -Ovarian Carcinoma, Fallopian Tube Cancer, Peritoneal Cancer, Breast Carcinoma -Unspecified Childhood Solid Tumor, Excluding CNS -Relapsed/Refractory Hematological Malignancies -Refractory Multiple Myeloma -etc. 	[136-162, 208, 209]
MLN8054	$C_{25}H_{15}ClF_2N_4O_2$	Aurora-A	Phase 1	<ul style="list-style-type: none"> -Benzodiazepine-like effects -Somnolence -Transaminitis 	<ul style="list-style-type: none"> -Asthenia -Anorexia -Fatigue -Insomnia -Confusion -Dizziness -Nausea 	<ul style="list-style-type: none"> -Advanced Solid Tumors -Breast Neoplasm, Colon Neoplasm, Pancreatic Neoplasm, Bladder Neoplasm 	[167-169]
MK-5108 (VX-689)	$C_{22}H_{21}ClFN_3O_3S$	Aurora-A (IC50: 0.064 nM)	Phase 1	<ul style="list-style-type: none"> -Febrile neutropenia -Infection 	<ul style="list-style-type: none"> -Blood and lymphatic system disorders -General disorders and administration site conditions -Gastrointestinal disorders 	<ul style="list-style-type: none"> -Advanced or Refractory Solid Tumors 	[170]

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AZD-1152 (Barasertib)	$C_{26}H_{31}FN_7O_6P$	Aurora-B	Phase 3	-Neutropenia -Stomatitis/mucositis	-Diarrhea -Fatigue -Infection -Nausea -Neutropenia -Pyrexia	-AML -Advanced Solid Tumors -Myeloid Leukemia -Relapsed/Refractory Diffuse Large B-cell Lymphoma	[210-217]
BI-831266	$C_{20}H_{14}O_2$	Aurora-B	Phase 1	-Febrile neutropenia	-Alopecia -Anemia -Dry skin -Fatigue -Nausea	-Advanced Solid Tumors	[218]
BI-811283	unknown	Aurora-B (IC50: 9 nM)	Phase 2	-Febrile neutropenia	-Fatigue -Leukopenia -Nausea	-AML -Advanced Solid Tumors	[219]

Part of the information comes from <https://clinicaltrials.gov/> and <https://pubchem.ncbi.nlm.nih.gov/>. Abbreviations: (i) DLT: dose-limiting toxicity, (ii) AE: adverse event, (iii) CML: chronic myeloid leukemia, (iv) SCLC: small-cell lung cancer, NSCLC: non-small-cell lung cancer (v) ALL: acute lymphoblastic leukemia (vi) AML: acute myeloid leukemia.

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achieve better efficacy than PD-L1 monotherapy [134].

Clinical application

Dozens of inhibitors of the Aurora kinase family are currently under development, many of which have entered into clinical trials and achieved promising results. (Table 1) (Figure 5, these structure diagrams come from PubChem: <https://pubchem.ncbi.nlm.nih.gov/>) These inhibitors can be roughly divided into four categories: (i) Aurora-A, Aurora-B, and Aurora-C inhibitors, consisting of PHA-79358 (danusertib), MK-0457 (VX-680, tozasertib), MSC19923-71A, ABT-348 (ilorasertib), BI-847325, and ENMD-2076; (ii) Aurora-A and Aurora-B inhibitors, consisting of AT9283, AMG900, and PF-03814735; (iii) specific Aurora-A inhibitors, consisting of MLN8237, MLN8054, and MK-5108 (VX-689); and (iv) specific Aurora-B inhibitors, including AZD-1152 (barasertib), BI-83-1266, and BI-811283. Here we focus on the specific Aurora-A inhibitors.

MLN8237, which is a second generation Aurora-A inhibitor, is currently in a phase 3 clinical trial. The main mode of administration is oral and its metabolites are mainly excreted from feces [135]. In the phase 1 and 2 clinical trial results, most of dose-limiting toxicities (DLTs) and the most common drug-related adverse events (AEs) were 1/2 grade adverse events, while 3/4 grade adverse events rarely occurred. Regarding the effectiveness of drug treatment, the overall response rate in lymphoma, NSCLC, pancreatic cancer, and esophageal cancer has been relatively optimistic, and the median progression-free survival (PFS) and time to progression (TTP) improved. The current phase 3 clinical trial of MLN8237 is mainly focused on hematologic tumors [136-161]. Unfortunately, phase 3 clinical research shows no prospective improvement of therapeutic effect using MLN8237 in relapsed or refractory peripheral T-cell lymphoma patients [162]. The clinical dose of MLN8237 has no effects on the QTc interval of patients [163]. Some researchers studied the effect of food on the effect of MLN8237 and found no difference in the distribution of MLN8237 after high-fat meals and in fasting states [164]. In advanced breast cancer and recurrent ovarian cancer, the combination of MLN8237 with paclitaxel

showed better therapeutic effect than paclitaxel monotherapy [165]. Some studies found that patients should avoid the simultaneous use of MLN8237 with gastric acid-reducing agents, potent CYP3A inhibitors, and strong metabolic enzyme inducers [166].

MLN8054 is a first generation Aurora-A inhibitor. It is currently in a phase 1 clinical trial and the main mode of administration is oral. The DLTs of MLN8054 are somnolence and transaminitis [167, 168]. In a phase 1 clinical study, it was found DLT with benzodiazepine-like effects [169].

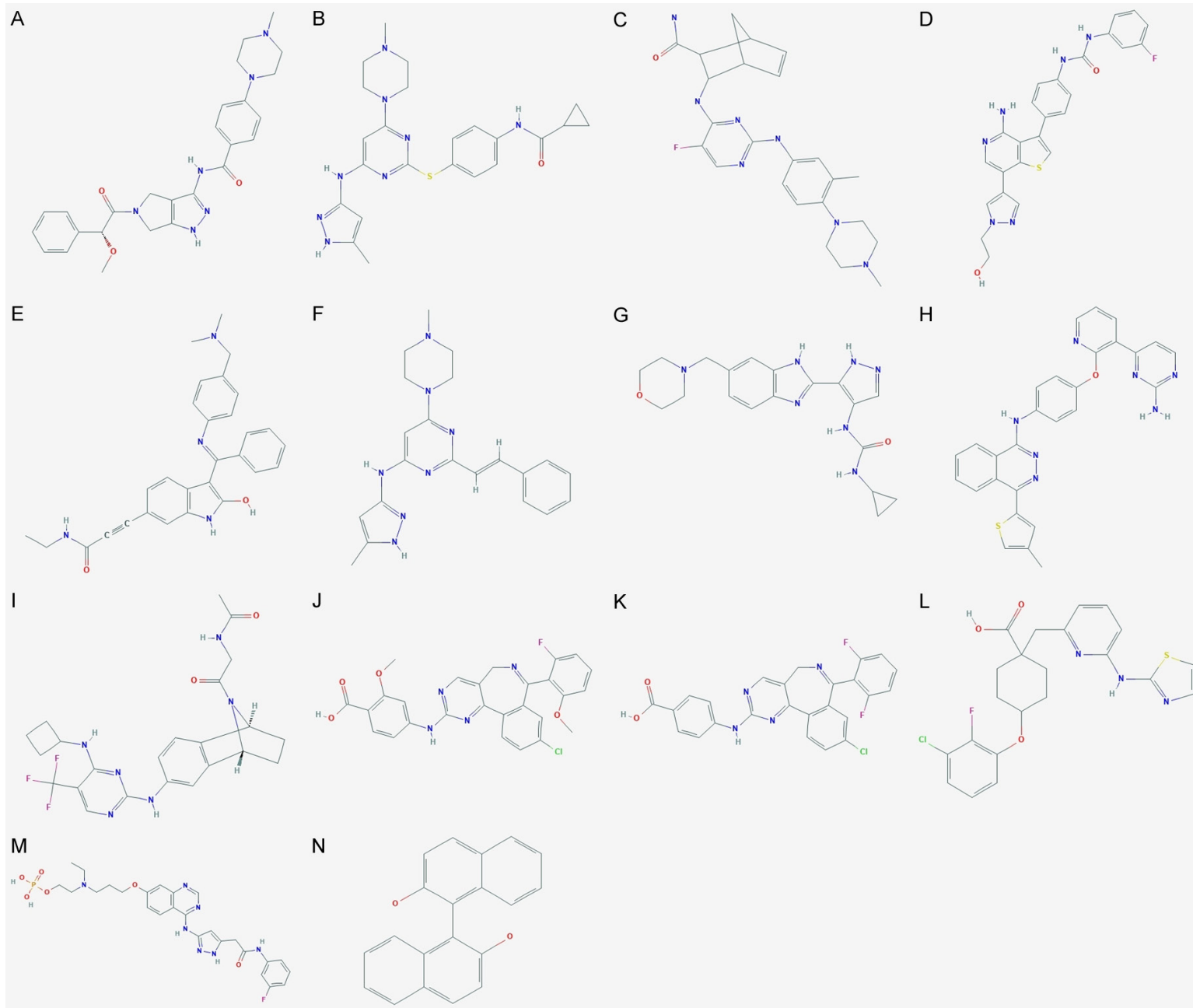
MK-5108 (VX-689) is currently in a phase 1 clinical trial and its treatment was associated with DLTs such as febrile neutropenia and infection and AEs including blood and lymphatic system disorders and gastrointestinal disorders [170].

Clinical trial results of first-generation inhibitors to second-generation inhibitors show that DLTs and AEs are continuously decreasing, which shows promise for the clinical use of Aurora-A inhibitors. Some studies have found that the functional single nucleotide polymorphism (SNP) of Aurora-A is related to the prognosis of patients with solid tumors and sensitivity to inhibitors [171-181].

Conclusion

Since the discovery of the Aurora kinase family in 1993, research on the Aurora kinase family has continued to increase and its clinical transformation is entering the final stage. The second-generation Aurora-A inhibitor MLN8237 has entered phase III clinical trials, which are mainly focused on hematologic malignancies. However, the single-agent treatment of MLN8237 showed limited benefit for patients, so the road to market of MLN8237 remains long. Aurora-A not only affects tumorigenesis and development, but also mediates tumor cell chemotherapy and radiotherapy resistance and participates in tumor immunotherapy. Thus, Aurora-A inhibitors have a wide range of clinical applications, not only as a therapeutic drug to kill tumor cells but also as an adjuvant drug in combination with other chemotherapy drugs or radiotherapy to improve the efficacy of existing treatments. Notably, the Aurora-A regulato-

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Figure 5. The chemical structure of Aurora kinase inhibitors. (From PubChem: <https://pubchem.ncbi.nlm.nih.gov/>). A. Structure of PHA-79358. B. Structure of MK-0457. C. Structure of MSC1992371A. D. Structure of ABT-348. E. Structure of BI-847325. F. Structure of ENMD-2076. G. Structure of AT9283. H. Structure of AMG900. I. Structure of PF-03814735. J. Structure of MLN8237. K. Structure of MLN8054. L. Structure of MK-5108. M. Structure of AZD-1152. N. Structure of BI-831266.

ry pathways in cells are very complex. It is unlikely that blocking one of them will completely prevent tumor progression and induce large-scale tumor cell apoptosis *in vivo*. Given that the combination of Aurora-A inhibitors and other antineoplastic drugs has achieved surprising anti-tumor effects in *in vitro* and *in vivo* experiments, the possibility of combining medications may be an effective strategy.

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Disclosure of conflict of interest

None.

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