Aurora-A Kinase: a Potent Oncogene and Target for Cancer Therapy

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Abstract

The Aurora kinase family comprises three serine/threonine kinases, Aurora-A, -B and -C. Among these, Aurora-A and -B play central roles in mitosis, whereas Aurora-C executes unique roles in meiosis. Overexpression or gene amplification of Aurora kinases have been reported in a broad range of human malignancies, pointing to their role as potent oncogenes in tumorigenesis. Aurora kinases therefore represent promising targets for anticancer therapeutics. So far, a number of Aurora kinase inhibitors (AKIs) have been generated, of which some are currently undergoing clinical trials. Recent studies have unveiled novel unexpected functions of Aurora kinases during cancer development and the mechanisms underlying the anticancer actions of AKIs. In this review, we discuss the most recent advances in Aurora-A kinase research and targeted cancer therapy, focusing on the oncogenic roles and signaling pathways of Aurora-A kinases in contributing tumorigenesis, the recent preclinical and clinical AKI data and potential alternative routes for Aurora-A kinase inhibition.

Key words: Aurora-A; Aurora kinase inhibitors (AKIs); targeted cancer therapy; mitosis; tumorigenesis

In mammals, the Aurora family of serine/threonine kinases consists of Aurora-A, -B and -C, which share a highly conserved catalytic domain containing auto-phosphorylating sites. The catalytic domain is flanked by a very short C-terminal tail and an N-terminal domain of variable lengths[1,2]. In the C-terminal regions of Auroras, there exists a short amino-acid peptide motif called "destruction box" (D-box). The D-box is recognized by the anaphase-promoting complex/cyclosome (APC/C) for degradation through the ubiquitin/proteasome-dependent pathway (Fig. 1A). Despite their structural similarities, the expression patterns, cellular localization and physiological functions of these three Aurora kinases are largely distinct. Aurora-A and -B are commonly expressed in most cell types whereas Aurora-C is specially expressed in the testis. Both Aurora-A and -B play key roles in regulating cell-cycle progression from G2 through to cytokinesis. Aurora-C has a unique physiological role in spermatogenesis and functions as a chromosomal passenger protein similar to Aurora-B in mitosis[2]. Overexpression of Aurora-A and -B have been found in multiple types of cancer (Table 1), which function as oncogenes to promote tumorigenesis, providing potential targets for cancer therapy. However, comparatively little information is available regarding the roles of Aurora-C in cancer. In this review, we will focus on recent progress as well as the main unresolved issues associated with Aurora-A in cancer.

1 FUNCTIONS OF AURORA-A

1.1 In normal cells

a. Mitosis

In G1 phase, the level of Aurora-A is rarely detectable. During S phase, a small proportion of Aurora-A is first detected at centrosomes. At late G2 phase, Aurora-A accumulates evidently at centrosomes and becomes activated [3]. During prometaphase and metaphase, active Aurora-A localizes on bipolar spindles and spindle poles after nuclear-envelope breakdown (NEBD). At the metaphase-anaphase transition, majority of Aurora-A is inactivated and degraded. A small fraction of Aurora-A remains on the centrosomes and the spindles at the onset of anaphase, and localizes to the spindle midzone and centrosomes during late anaphase and telophase/cytokinesis (Fig.1B and C) [2,4].

Aurora-A is required for execution of a sequence of key mitotic events, such as centrosome maturation, mitosis entry, mitotic spindle formation and cytokinesis. Aurora-A induces phosphorylation of TACC, leading to the complex formation with XMAP215 promoting centrosomal microtubule stabilization[5,6]. Prior to the initiation of M-phase, Aurora-A couples with its partner Bora to induce phosphorylation and activation of PLK1[7]. This finding first clarified the sequential interaction between Aurora-A and PLK1 in mitotic entry. Activated PLK1 then renders the activation of CDK1/cyclin B through degrading the CDK-inhibitory kinase WEE1 and activating phosphatase CDC25C. Aurora-A also activates another CDK-activator, the phosphatase CDC25B phosphorylation, further supporting its role in enhancing G2/M transition[8-10]. In addition, a LIM protein called Ajuba which is phosphorylated by Aurora-A,

induces activation of Aurora-A at late G2, forming a positive feedback loop to initiate mitosis[3]. In prophase, Aurora-A promotes nuclear envelope break down (NEBD)[11] and induces the phosphorylation of Eg5, a kinesin-like motor to enhance centrosome separation[12]. Yet, the detailed mechanism for these critical events remains unknown. At the initiation of bipolar spindle formation, there also exists a positive feedback loop between Aurora-A and TPX2, depletion of either of which causes defect formation of spindles[13-16]. Aurora-A is also directly involved in metaphase chromosome alignment by phosphorylating CENP-A at Ser7 for subsequently Aurora-B-dependent phosphorylation of CENP-A and kinetochore function[17]. Moreover, Aurora-A phosphorylates CENP-E, resulting in delivery of PP1 to the kinetochore for the stable bi-orientation of chromosomes[18]. Thus, members of Aurora kinase family appear to cooperate in regulating kinetochore function. At spindle checkpoint, Aurora-A induces phosphorylation and proteasomal degradation of RASSF1A, relieving RASSF1A-dependent inhibition of the APC/Cdc20 complex and culminates in APC/Cdc20 activation to promote cell cycle progression[19]. During anaphase, Aurora-A induces phosphorylation at p150(Glued) Ser19 and TACC Ser558 in assembling central spindle[20,21]. At the end of mitosis, the degradation of Aurora-A by the APC/Cdh1 complex is required for proper cytokinesis and mitotic exit[22,23]. Taken together, Aurora-A has been demonstrated to participate in many important events of mitosis, indicating dysregulation of Aurora-A would cause aberrant cell cycle.

b. Asymmetric division

Aurora kinases play crucial roles in the regulation of cell polarity and asymmetric

division[24-27]. Activated Aurora-A kinase is responsible for the asymmetric localization of Numb, an important cell fate determinant and negative regulator of Notch signaling. Aurora-A activates the atypical protein kinase C (aPKC) by phosphorylating Par-6. Following this event, aPKC phosphorylates and releases Numb from one side of the cell cortex into one of the two daughter cells, which causes Drosophila neural precursor asymmetrical cell division[25]. Loss of Aurora-A leads to defects in asymmetric Numb localization and spindle-to-cortical polarity alignment, which suppresses self-renewal of neuroblasts and promotes neuronal differentiation[26].

c. Cilia dynamics

Primary cilia are known to be regulated dynamically throughout the cell cycle. Aurora-A negatively regulates ciliary dynamics in proliferating cells, and its activity outside mitosis is required for two aspects. First, Aurora-A promotes ciliary resorption (disassembly) at cell cycle re-entry. In G0 phase, Aurora-A interacts with enhancer of filamentation 1 (HEF1/NEDD9) to phosphorylate and activate histone deacetylase 6 (HDAC6), which in turn removes acetylated group on axonemal α-tubulin and causes the disassembly of the primary cilia[28]. Ca^{2+}/CaM is found to enhance the binding between Aurora-A and HEF1, which in turn activates Aurora-A[29], while NPHP2 directly interact and inhibit Aurora-A[30]. In the setting of VHL deficiency, elevated Aurora-A expression is driven by activated β-catenin[31]. Both of the above signals regulate ciliary disassembly through the HEF1/Aurora-A module. In addition, Pitchfork is assumed to physically interact with Aurora-A during cilia disassembly in a way similar to HEF1[32]. Second, Aurora-A continuously suppresses cilia regeneration during cell proliferation. As HEF1 levels decreased in

G1 phase, the trichoplein/Aurora-A pathway which inhibits cilia formation, is required for G1 progression[33].

1.2 In cancer cells

Recently, the studies of Aurora-A expression pattern in cancer tissues have demonstrated that Aurora-A is overexpressed and diffusely distributed in both nucleus and cytoplasm, regardless of their cell-cycle phases[34]. The aberrant expression and localization of Aurora-A strongly implies that Aurora-A promotes tumorigenesis, very likely through distinct mechanisms (Fig.2). Aurora-A plays multiple roles in regulating cancer development *via* promoting cell cycle progression, activating cell survival and/or anti-apoptosis signaling, enhancing tumorigenicity of oncogenes, and contributing to EMT and stem-like properties of cancer cells. The oncogenic roles of Aurora-A may vary in different types of cancer. In neuroblastomas with MYCN gene amplification, the function of Aurora-A stabilizing N-Myc and preventing N-Myc degradation might be most important. In contrast, in majority of leukemia and solid tumors, the cell cycle relevant functions of Aurora-A as overriding cell cycle checkpoints and promoting cell cycle progression seems to be dominated. As the expression pattern of Aurora-A in cancer is distinguished from that in normal cells, it is possible that Aurora-A may promote tumorigenesis through excessive functions in cancer cells. Importantly, the deregulation of functional balance between Aurora-A and p53 family is involved in cell cycle checkpoint abnormalities, chromosome instability, cell growth and drug-resistance, as well as self-renewal of CSCs. Thus, the interaction of Aurora-A and p53 at multiple levels should be taken into account in targeting

Aurora-A for cancer therapy.

a. Proliferation

Uncontrolled proliferation is a hallmark of cancer cells. Aurora-A has been found to promote cell cycle progression through repealing suppressors and/or enhancing promoters of cell cycle. For example, inhibition of Aurora-A in ovarian cancer cells increases the expression of retinoblastoma protein (pRb), and attenuates G1/S transition [35]. Consistently, Aurora-A inhibitor MLN8237 induces senescence in cancer cells is associated with upregulation/stabilization of p53, p21, and hypophosphorylated pRb [36]. In addition, Aurora-A associates with and phosphorylates RASSF1A on Thr202 and/or Ser203, which restricts with RASSF1A-mediated growth suppression in human tumors [37,38].

Moreover, in a cyclin B2 transgenic mice model, overexpression of cyclin B2 significantly accelerates centrosome separationleads to aneuploidy and tumorigenesis, which is associated with Aurora-A mediated hyperactivation of PLK1 [39]. Specifically, this function of cyclin B2 is antagonistically regulated by p53, which inhibits Aurora-A expression and kinase activity. Thus, uncontrolled cell cycle progression is involved in Aurora-A promoted tumorigenesis.

b. Genomic instability

The cell cycle checkpoints ensure the proper cell division, which is essential for maintaining the genomic stability. Overexpression of Aurora-A induces the disruption of checkpoints, leading to aneuploidy and genomic instability, a hallmark of malignant transformation. First, Aurora-A contributes to the abrogation of G2/M DNA damage checkpoint. Overexpression of

Aurora-A abrogates the G2/M DNA damage checkpoint by inducing constitutive activation of CDK1 in cancer cells [40,41]. Moreover, Aurora-A promotes G2/M transition by phosphorylating BRCA1 at Ser308 [42]. Inhibition of Aurora-A increases BRCA1/2 expression[35,43], consistent with the finding that a negative correlation between Aurora-A and BRCA2 expression in human ovarian carcinoma [35,44]. Further studies show that Aurora-A and BRCA1/2 inversely control the sensitivity to radio- and chemotherapy through the ATM/Chk2-mediated DNA repair networks[45].

In addition, the mitotic spindle apparatus is a major target in chemotherapy. Paclitaxel interferes with microtubule dynamics and arrests cell cycle through activation of the spindle assembly checkpoint (SAC). Overexpression of Aurora-A induces dysfunction of SAC, causing resistant to paclitaxel-induced apoptosis in tumor cells[46]. Moreover, Aurora-A abrogates p73 functions in DNA damage response and SAC pathways. Specifically, p73 forms a cytoplasmic ternary complex with the inhibitory checkpoint proteins Mad2 and CDC20. Phosphorylation of p73 by Aurora-A at Ser235 causes dissociation of the Mad2-CDC20 complex, thus inactivates mitotic SAC and leads to mitotic exit[47]. Conversely, in p53-deficient cancer cells, inhibition of Aurora-A leads to p73 activation and up-regulation of p73 down-stream target genes during induction of cell death[48]. Thus, disruption of checkpoints is involved in Aurora-A induced genomic instability.

c. Anti-apoptosis

Aurora-A promotes cancer cell survival through modulating survival signaling pathways. Aurora-A has been implicated in the activation of NF-κB signaling *via* physical interactions with

IKK kinases (IKKα and IKKβ) and the phosphorylation of IκBα[49-54]. Aurora-A also induces cell survival and chemoresistance by activation of PI3K/Akt/GSK3 signaling cascades. For example, Aurora-A protects ovarian cancer cells from apoptosis induced by chemotherapeutic agents such as cisplatin, etoposide and paclitaxel by activating Akt pathway. In concordance, inhibition of Aurora kinases suppresses Akt activation, induces apoptotic cell death and overrides drug resistance in AML cells[54-57].

Aurora-A also contributes to anti-apoptosis via regulating the modulators of apoptosis. Our laboratory discovers that inhibition of Aurora-A increases Bax/Bcl-2 expression ratio, a favorable pro-apoptotic predictor for drug response in AML[58]. The expression of PUMA, another modulator of apoptosis, is significantly increased after suppression of Aurora-A by siRNA or small-molecule inhibitors[59]. Inhibition of Aurora-A also induces the expression of the pro-apoptotic protein Bim and triggers apoptosis in AML cells. Accordingly, pro-apoptotic signals are down-regulated by Aurora-A through the phosphorylation and degradation of BimEL, which is the major splice variant of Bim[60,61]. Thus, Aurora-A cooperates with different signaling pathways to maintain cell survival through suppressing apoptosis.

In addition, Aurora-A promotes cell survival by suppressing autophagy. In either nutrient deprivation or normal conditions, overexpression of Aurora-A inhibits autophagy through activating mTOR signaling. For example, phosphorylation of both RPS6KB1 and mTOR is elevated by overexpression of Aurora-A whereas suppressed by depletion or inhibition of Aurora-A in breast cancer [62]. Moreover, inhibition of mTOR by PP242 abrogates the changes of LC3-II as well as autophagy-associated protein SQSTM1(p62) induced by

AURKA-overexpression. Consistently, a positive correlation between Aurora-A and p62 is found in breast cancer[62,63]. Hence, drug combination with Aurora-A inhibitors targeting autophagy may be deeply explored in future clinical cancer therapy.

d. EMT, migration and invasion

Overexpression of Aurora-A is involved in multiple critical steps of tumor invasion and metastasis. First, Aurora-A promotes epithelial-mesenchymal transition (EMT) through inducing SLUG, FBN1 expression, while suppressing E-cadherin, β-catenin and p53[64]. Consistently, our previous study shows that inhibition of Aurora-A restores membrane expression of E-cadherin and β-catenin, suggesting a reversed mesenchymal-epithelial transition process in cancer cells[65].

Second, Aurora-A promotes tumor cell migration and invasion through activating several oncogenic signaling including AKT[66], MAPK[65], Coffilin-F-actin[67], SRC[68], focal adhesion kinase (FAK)[69] pathways. For example, overexpession of Aurora-A increased the expression of the cofilin phosphatase Slingshot-1 (SSH1), contributing to cofilin activation and cell migration[67]. On the other hand, oncogenic factors contribute to cancer cell migration and invasion *via* activation and/or accumulation of Aurora-A. For example, the hypoxia-inducible factor 1α (HIF-1α) transcriptionally upregulates Aurora-A expression by binding to and activating hypoxia responsive elements (HRE) of AURKA promoter, overexpressed Aurora-A then enhances hepatocelluar carcinoma cells migration [70]. Additionally, the Raf-1 signaling induces the stabilization and accumulation of Aurora-A, which subsequently induces phosphorylation and nuclear translocation of SMAD5, contributing to distant metastasis [64].

Third, overexpressed Aurora-A is involved in extracellular matrix degradation, by which tumor cells overcome physical barriers to cell invasion and extravasation. For example, overexpression of Aurora-A enhances the expression and secretion of matrix metalloproteinases (MMP)-2 associating the activation of p38 MAPK and Akt signaling[71]. Similarly, overexpression of Aurora-A increases both mRNA and protein levels of MMP-7 and MMP-10, consistent with the finding that a significant positively correlation among Aurora-A, MMP-7 and MMP-10 expressions in head and neck cancer[72]. Thus, Aurora-A plays a critical role in regulating tumor cell mobility, providing a potential target for preventing cancer metastasis.

e. Stemness

Cancer stem cells (CSCs) are a distinct subset of cancer cells with self-renew and cancer-reconstitution capacity[73]. Aurora-A overexpression is observed in CSC-enriched populations, including breast cancer[64], ovarian cancer[50], acute myelogenous leukemia (AML)[74] and mesenchymal stem cells (MSCs) from myelodysplastic syndromes (MDS) patients[75]. Consistent overexpression of Aurora-A in CSCs indicates a critical role in cancer stem-like properties (eg. therapy-resistance, tumorigenesis and EMT). Indeed, Aurora-A inhibition has been shown to impair stem-like functions in various cancers including ovarian cancer[50], AML[74], chronic myeloid leukemia (CML)[76], breast cancer[77], glioma[78] and glioblastoma[79,80]. The interaction between Aurora-A and Wnt-β-catenin pathway is involved in CSCs regulation in both CML and head and neck cancer[81]. The β-catenin/TCF4 complex transcriptionally activates AURKA, and Aurora-A in turn inhibits GSK3β, stabilizes β-catenin and further strengthens the

core signaling for stemness.

Moreover, Aurora-A regulates CSCs not only in cytoplasm but also in nucleus. Nuclear-localized Aurora-A is observed in both CML[76] and colorectal cancer stem cells[82]. Indeed, overexpression of Aurora-A induces the expression of core stem cell factors including MYC, SOX2[64] and OCT4[77]. Notably, we have recently disclosed a new function of nuclear Aurora-A, as a trans-activating factor to induce MYC gene expression in a kinase independent manner, by which Aurora-A promotes breast CSCs phenotype[83]. Thus, Aurora-A promotes CSCs through both conical and non-conical mechanisms.

1.3 Oncogenic interacting molecules

There are more than 140 molecules interacting with Aurora-A, including substrates of Aurora-A and its activators and inhibitors, as well as the proteins that are involved in the transcription or degradation of Aurora-A (http://cpdb.molgen.mpg.de/CPDB). In cancer, Aurora-A integrates its functions with multiple oncogenic and tumor suppressive proteins to promote tumorigenesis.

a. Interaction with tumor suppressors(Fig.3)

The interaction between Aurora-A and p53 has been intensively studied. Aurora-A suppresses p53 function through inducing phosphorylation of p53. Phosphorylation (Ser315) of p53 by Aurora-A induces MDM2-mediated destabilization of p53[84]. In addition, Aurora-A phosphorylates p53 at Ser215, leading to abrogation of p53 DNA binding and transactivation activity[85]. In a feedback loop, p53 negatively regulates Aurora-A both transcriptionally and

posttranslationally[86]. In p53 deficient cells, CDK2 is activated by reducing $p21^{Cip1}$ expression, resulting in pRb hyperphosphorylation and its dissociation from transcriptional factor E2F3. E2F3 then binds to the *AURKA* gene promoter and transactivatesAurora-A expression. Deficiency in p53 also causes the downregulation of Fbw7α, a component of E3 ligase targeting Aurora-A for degradation[86]. Moreover, p53 suppresses the oncogenic activity of Aurora-A in a transactivation-independent manner. Indeed, p53 inhibits Aurora-A kinase activity *via* direct interaction with the latter's Aurora box [87]. Thus, the reciprocal relationship between Aurora-A and p53 might have important implications for anticancer therapy.

b. Interaction with oncogenic proteins(Fig.4)

MYC proteins are major drivers of a range of cancers. Deregulation of MYCN expression is implicated in the development of neuroblastoma. Aurora-A forms a complex with the oncogenic N-Myc protein, which protects N-Myc from proteasomal degradation mediated by the Fbxw7 ubiquitin ligase[88]. Moreover, Aurora-A-mediated stabilization of N-Myc up-regulates VEGF expression and promotes angiogenesis in neuroblastomas[89]. The Aurora-A inhibitors MLN8054 and MLN8237 disrupt this Aurora-A/N-Myc complex and promotes N-Myc degradation, leading to tumor regression and prolonged survival in a mouse model of Myc-driven neuroblastoma[90]. Similarly, the other Aurora kinase inhibitor, CCT137690, decreases N-Myc protein expression and sensitizes *MYCN*-amplified neuroblastoma *in vivo*[91]. So far, a class of conformation-disrupting inhibitors of Aurora-A that destabilizes interactions between Aurora-A and MYCN has shown effect of driving degradation of MYCN protein *in vitro* and *in*

vivo, across MYCN-driven cancers[92], which delineates a kinase-independent function of Aurora-A on proteolytic degradation of MYCN. Concurrent *AURKA* and *MYCN* gene amplifications are clinical indications of lethal treatment-related neuroendocrine prostate cancer[93]. Recently, LIN28B, which promoting MYCN expression, has been identified as a predisposition gene and an oncogenic driver in neuroblastoma subsets. Further study has found that LIN28B coordinates the expression of the oncogenes RAN and AURKA to promote neuroblastoma tumorigenesis [94].

In addition, Aurora-A enhances both the expression and transcriptional activity of c-Myc[95]. Specifically, nuclear Aurora-A forms a complex with hnRNPK on *MYC* promoter, which activate *MYC* transcription[83]. Conversely, c-Myc regulates Aurora-A expression by directly inducing its transcription in Myc-driven B-cell lymphomas[96]. Accordingly, the Myc transcription factor and its Max binding partner are associated with *AURKA* promoter during the G2 phase of the cell cycle[97]. Thus, targeting Aurora-A could have the potential to block other undruggable oncoprotein as MYC.

2. ABERRANT AURORA-A IN CLINICAL PROGNOSIS

2.1 Aberrant Aurora-A in survival

Aurora-A overexpression predicts adverse prognosis in a number of malignancies. In node-negative breast cancer patients, Aurora-A expression is associated with worse prognosis in carcinomas with the molecular subtype ER+/HER2- but not in ER-/HER2- or in HER2+ carcinomas[98]. Moreover, Aurora-A outperforms other proliferation markers, like Ki67, as an independent predictor for breast cancer-specific survival in ER-positive breast cancer patients, suggesting its potential use in routine clinical practice[99]. Furthermore, nuclear expression of Aurora-A is correlated with expression of both oestrogen and progesterone receptors in breast cancer and predicts poor clinical outcome in ovarian cancer[100]. In addition, increased Aurora-A gene copy number is associated with poor outcome among patients with KRAS wild-type metastatic colorectal cancers[101]. In agreement, we have described a negative correlation between Aurora-A overexpression and median survival time in laryngeal squamous cell carcinoma patients[66]. In non-small cell lung cancer, Aurora-A expression is significantly up-regulated in tumor samples and is associated with tumor de-differentiation[102].

2.2 Aberrant Aurora-A in metastasis and drug-resistance

Recent studies indicate that Aurora-A is a reliable biomarker for accurate risk definition in metastasis and drug resistance. Our laboratory has shown that Aurora-A expression predicts the risk of distant metastasis and promises a potential therapeutic target in triple-negative breast cancer[103]. We and others have found that Aurora-A expression is positively correlated with

clinical stage, cranial bone and local invasion, as well as poor survival, in nasopharyngeal carcinoma[65,104]. Additionally, Aurora-A is an important factor for predicting clinical outcome and the presence of vascular invasion in urothelial carcinomas[105]. Overexpression of Aurora-A protein correlates with the invasive malignancy of esophageal squamous cell carcinoma[106]. Moreover, the correlation between Aurora-A polymorphisms and clinical outcomes in esophageal cancer has also been investigated. The variant Phe31/Ile has an adverse effect on the response to cisplatin-based therapy, whereas the variant 91A-169G haplotype carries a significant risk for a lack of a complete response and a higher rate of recurrence[107]. As summarized in Table 1, Aurora-A is overexpressed in numerous types of cancer and its expression is associated with poor patient prognosis. These findings make the *AURKA* gene a strong candidate as a low-penetrance tumor-susceptibility gene in both mice and humans[108].

3. TARGETING AURORA-A KINASE

Because of the important roles of Aurora-A kinase in tumorigenesis, numerous AKIs have been developed. Indeed, these AKIs are in various stages of preclinical and clinical evaluations, and some have yielded encouraging results (Table 2).

3.1 AKIs

3.11 Specific Aurora-A kinase inhibitors

MLN8054

An unprecedented kinase inhibitor framework has been developed for a compound known as MLN8054. It has a benzazepine core scaffold with a fused amino pyrimidine ring and an aryl carboxylic acid. It is an ATP-competitive, reversible inhibitor of recombinant Aurora-A kinase with high specificity (IC_{50} of 4 nM). MLN8054 exhibits a selectivity of >40-fold for Aurora-A compared with another family member Aurora-B[109]. In both human HCT-116 colorectal and PC-3 prostate tumor cells, treatment with 1 μM MLN8054 delays G2/M progression. MLN8054 effectively inhibits the growth of multiple human cancer cell types (IC_{50} values ranging from 0.11 to 1.43 μM). MLN8054 significantly inhibits the growth of PC-3 tumor xenografts in nude mice at doses of 30 mg/kg QD and BID [tumor growth inhibition (TGI), 81%, and 93%]. Remarkably, TGI is sustained even after treatment is withdrawn[109]. In addition, MLN8054 can induce senescence in HCT-116 cells both *in vitro* and *in vivo*. This effect is related to the up-regulation and stabilization of p53 and $p21^{Cip1}$, and the hypophosphorylation and inactivation of pRb[36]. Further, MLN8054 can confer radio-sensitivity to androgen-insensitive prostate cancer cells *in vitro* and *in vivo*[110].

A phase I study of MLN8054 in patients with advanced solid tumors has been promising. It defines an estimated maximum tolerated dose (MTD) of 60 mg QID/M for 14 days. MLN8054 is absorbed rapidly, the exposure dose proportional, and the terminal half-life 30-40 h. Three (5%) patients had stable disease for >6 cycles[111]. Mitotic cells in skin and tumor biopsies obtained from patients who received MLN8054 orally for 7 consecutive days exhibited defects in chromosome alignment and spindle bipolarity, which are new biomarkers of Aurora-A inhibition independent of mitotic arrest or slippage[112]. However, only some patients were shown able to maintain a steady-state plasma concentration of 2 μM, which is estimated to be necessary for antitumor activity.

MLN8237

MLN8237 (Alisertib) was developed by Millennium Pharmaceuticals Company from the predecessor MLN8054. MLN8237 is a second-generation compound and the first orally bioavailable, highly selective small molecule inhibitor of Aurora-A kinase, with an IC_{50} of 1 nM (Sells T, AACR Annual Meeting, 2008). MLN8237 binds to and inhibits Aurora-A kinase in cells with selectivity over Aurora-B kinase of greater than 200-fold. It functions by disrupting the assembly of the mitotic spindle apparatus and chromosomal segregation, and also through inhibiting cell proliferation *in vitro* and tumor growth in solid tumor xenograft models[113].

MLN8237 was tested against the Pediatric Preclinical Testing Program (PPTP) *in vitro* panel and exhibited a high efficacy (median IC_{50} of 61 nM)[114], particular towards ALL cell lines. While ALL cell lines were more sensitive and the rhabdomyosarcoma cell lines less sensitive to

MLN8237 compared to other PPTP cell lines. Moreover, high levels of *in vivo* activity were also observed against the ALL xenograft panel. MLN8237 significantly increased event-free survival (EFS) compared with controls in the majority of solid tumor models (32/40; 80%) and all (6/6; 100%) the ALL xenografts. Maintained complete responses (CRs) were also observed in a high number of neuroblastoma xenografts (3/7) [114]. MLN8237 has also been reported to induce early apoptosis of human T-cell leukemia virus type 1 (HTLV-1)-infected T-cell lines without the induction of polyploidy, and is associated with the activation of a p53-dependent post-mitotic G1 checkpoint[115].

Treatment of cultured multiple myeloma (MM) cells with MLN8237 (0.5 μM) inhibits the phosphorylation of Aurora-A kinase rather than Aurora-B-mediated histone H3 phosphorylation[116]. MLN8237 inhibits the proliferation of MM cells and can overcome the protective effect of the BM environment on MM cells *in vitro* (IC_{50}: 0.003-1.71 μM). MLN8237 also induces a 2- to 6-fold increase in cells at the G2/M phase cell population, apoptosis and senescence in MM cells and this is related to the upregulation of p53, $p21^{Cip1}$ and $p27^{Kip1}$ expression[116]. MLN8237 is also synergistic with dexamethasone (CI<1) and additive/synergistic with doxorubicin or bortezomib (CI±1) against the human multiple myeloma OPM1 cells. In MM cells, MLN8237 activates stress-activated protein kinase (pSAPK/JNK; Thr183/Tyr185) phosphorylation, but downregulates phosphorylation of Cell division cycle 2 (Cdc2; Tyr15) and Checkpoint 1 (Chk1; Ser345) proteins[116]. In an MM xenograft murine model, tumor burden was significantly reduced, and overall survival significantly prolonged in animals treated with MLN8237 (30 mg/kg for 21 days) compared with controls. Importantly, there were no significant

changes in weight or signs of toxicity or infection in animals receiving MLN8237[116], suggesting minimum side effects.

MLN8237 has also been evaluated against chronic myeloid leukemia (CML) cells expressing non-mutated and mutated forms of BCR-ABL (breakpoint cluster region-Abelson kinase). MLN8237 treatment disrupts cell cycle kinetics and induces apoptosis by reducing the expression of the large inhibitor of apoptosis protein Apollon, which promotes the efficacy of nilotinib *in vitro* and *in vivo*. In contrast to other Aurora kinase inhibitors, MLN8237 does not significantly affect BCR-ABL activity[117].

In addition, treatment with MLN8237 also inhibits peripheral T-cell lymphomas (PTCL) cell proliferation (IC_{50}: 80-100 nM). MLN8237 induces endoreduplication and apoptosis correlated with inhibition of histone H3 and Aurora-A phosphorylation in these T-cell lymphomas[118]. MLN8237 has also been tested recently in malignant bladder cancer cells *in vitro* and *in vivo* models, where it induces cell cycle arrest, aneuploidy, mitotic spindle failure, and apoptosis. It also acts synergistically with either paclitaxel or gemcitabine *in vitro* to cause cell death. MLN8237 also inhibits bladder cancer tumor growth when administered orally in a mouse bladder cancer xenograft model[119]. Furthermore, MLN8237 potently inhibits the proliferation of tumor stem-like cells and potentiates the effects of temozolomide and ionizing radiation in glioblastoma[80].

A number of phase I and II studies have been carried out on MLN8237 to establish the safe dose range, the side effects and potential efficacy of the drug. A phase I study of MLN8237 in patients with advanced solid tumors establishes the MTD for the 7- and 21-day schedules as 50

mg twice daily and 50 mg once daily, respectively[120]. Another pediatric phase I trial and pharmacokinetic study shows that children can tolerate high doses of MLN8237 (80 mg/m^2/d once daily for 7 days)[121]. After MLN8237 treatment, stable disease has been observed with durable effects with repeated treatment cycles over 6 months[120]. In another phase I study in adults (87 patients) with advanced solid tumors, one MLN8237 treated patient (1%) achieved a partial response lasting for more than 1 year, whereas 20 (23%) patients achieved stable disease for ≥3 months[122]. Phase II trials of MLN8237 in patients with ovarian, fallopian tube, peritoneal carcinoma, acute myelogenous leukemia and high-grade myelodysplastic syndrome have also been carried out and completed. Responses of 6.9-11.1 months in duration were observed in 3 (10%) patients with platinum-resistant ovarian cancer, whereas 16 (52%) patients achieved stable disease with a mean duration of response of 2.86 months[123]. A phase II study of investigational MLN8237 in acute myelogenous leukemia and myelodysplastic syndromes reveals that AKI may induce leukemic cell senescence[124]. Recently, a phase II study to investigate the safety and activity of single-agent MLN8237 in patients with predefined muti-types of advanced solid tumors has been completed (NCT01045421) [125]. The objective response was reported as nine (18%, 95% CI 9-32) of 49 women with breast cancer, ten (21%, 10-35) of 48 participants with small-cell lung cancer, one (4%, 0-22) of 23 patients with non-small-cell lung cancer, four (9%, 2-21) of 45 people with head and neck squamous-cell carcinoma, and four (9%, 2-20) of 47 individuals with gastro-oesophageal adenocarcinoma; all were partial responses. Adverse events were similar across tumor types[68]. In fact, MLN8237 is the first oral selective Aurora-A kinase inhibitor to enter phase III clinical trials and is currently being assessed in patients with relapsed

or refractory peripheral T-cell lymphoma (NCT01482962).

ENMD-2076

ENMD-2076, developed by EntreMed, is another potent and selective inhibitor of Aurora-A and Flt3 (IC_{50} values of 14 and 1.86 nM), as measured by biochemical assays. It is the tartrate salt of a vinyl-pyrimidine free base previously referred to as ENMD-981693 or MKC-1693. This molecule also inhibits 15 other oncogenic kinases including multiple kinases involved in angiogenesis, such as VEGFR2/KDR, VEGFR3, FGFR1, FGFR2, and PDGFRα with IC_{50} values of less than 100 nM. ENMD-2076 is not significantly active against Aurora-B kinase (IC_{50}=350 nM)[126].

The activity of ENMD-2076 has been evaluated against cell lines derived from both hematological and solid tumors using *in vitro* assays. ENMD-2076 effectively inhibits the proliferation of solid tumor cell lines (mean IC_{50} value of 0.4 nM) and leukemia cell lines (IC_{50} values ranging from 0.025 to 0.53 nM). Crucially, among this panel, the biphenotypic B-myelomonocytic leukemia cell line MV4-11, which expresses the Flt-3 internal tandem duplication mutation[127], is the most sensitive, indicating its high specificity and potency of ENMD-2076 for Aurora-A and Flt-3[126]. In these tissue culture models, ENMD-2076 induces a dose-dependent increase in G2/M phase arrest and subsequent apoptotic cell death, consistent with its selective inhibition of Aurora-A rather than Aurora-B[126]. ENMD-2076 has also been observed to induce G2/M cell cycle arrest and dose-dependent cytotoxicity faster and more efficiently than radiation treatment alone in canine mast cell tumor cell lines[128].

ENMD-2076 can also induce regression or complete inhibition of tumor growth *in vivo* at well-tolerated doses in tumor xenograft models derived from breast carcinoma, colon cancer, melanoma, leukemia, and multiple myeloma cell lines. For example, treatment with 75 mg/kg ENMD-2076 can inhibit tumor growth in a breast cancer MDA-MB-231 xenograft model (TGI=54%), and at a higher dose (302 mg/kg) it can almost completely abrogates tumor growth (TGI=99%). In both cases, ENMD-2076 treatment is also accompanied by a substantial decrease in vessel density[126]. The activity of ENMD-2076 against multiple myeloma (MM) has also been tested both *in vitro* and *in vivo*. ENMD-2076 displays extensive cytotoxicity against MM cell lines (IM9, ARH-77, U266, RPMI 8226, MM.1S, MM.1R, NCI-H929) and primary MM cells derived from patients, with minimal cytotoxicity against hematopoietic progenitors. Inhibition of the PI3K/AKT pathway and downregulation of survivin and X-linked inhibitor of apoptosis (XIAP) have been observed almost immediately (6 h) after treatment. Oral treatment with ENMD-2076 (50, 100, 200 mg/kg/d) can result in a dose-dependent inhibition of tumor growth in a H929 human plasmacytoma xenograft model. A significant reduction in phospho-histone H3 (pH3), Ki-67, p-FGFR3 and angiogenesis as well as a significant increase in cleaved caspase-3 were observed in tumors[129].

Data from the one phase I clinical trial with ENMD-2076 given orally (once-daily 60-200 mg/m^2) to 67 patients with ovarian cancer, colorectal cancer, or refractory advanced solid malignancies, are now available. The results show that ENMD-2076 is generally well tolerated (MTD=160 mg/m^2), but hypertension and neutropenia are also observed in small number of patients (2 patients at 200 mg/m^2). Decreased plasma sVEGFR2 is observed in patients

post-treatment. Intriguingly, two patients with platinum refractory/resistant ovarian cancer have shown RECIST partial responses, indicating a potential application for ENMD-2076 in platinum resistant ovarian cancer patients. ENMD-2076 demonstrates a linear pharmacokinetic profile with a rapid absorption phase (T_{max}=3-7.8 h) and a relatively long half-life ($t_{1/2}$ of 27.3 to 38.3 h after a single dose) [130]. A phase II study of ENMD-2076 in previously treated locally advanced and metastatic triple-negative breast cancer is ongoing (NCT01639248).

3.12Pan-Aurora kinase inhibitors

VX-680 (Tozasertib, MK-0457)

VX-680, developed by Vertex Pharmaceuticals, Cambridge, MA, is a highly potent, selective and reversible inhibitor that targets the ATP-binding sites of Aurora-A, -B and -C (K_i values of 0.6, 18 and 4.6 nM, respectively)[131]. VX-680 causes the accumulation of cells with ≥4N DNA content and inhibits histone H3 phosphorylation at Ser10. It also inhibits cell cycle progression and proliferation, and induces apoptosis in a wide variety of tumor cell types (IC_{50} values ranging from 15 to 113 nM). VX-680 can also abolish the colony formation ability of primary leukemic cells possessing internal tandem duplication (ITD) mutations of FLT3[131]. Consistent with these results, we have demonstrated that VX-680 induces apoptosis in acute myeloid leukemia with the FLT3/ITD mutation[58].

When used in nude mice xenograft models, VX-680 treatment causes substantial reductions in tumor sizes (75 mg/kg/2d for 13 days; the TGI: 98%). A higher dose of VX-680 (2 mg/kg/h) yields even better efficacy, with a compelling 56% decrease in mean tumor volume[131].

Furthermore, in one study VX-680 exhibits potent inhibitory activity against BCR-ABL bearing the T315I mutation in patient samples[132]. In another study, VX-680 has been shown to display significant effects on primary human Philadelphia chromosome-positive ALL (Ph+ALL) cells both with and without the T315I mutation. VX-680 inhibits the tyrosine phosphorylation downstream of BCR-ABL, and induces apoptosis in Ph+ALL cells[133]. VX-680 also promotes apoptosis in imatinib-resistant primary CML specimens expressing the T315I and other BCR-ABL mutations without affecting the wild-type BCR-ABL kinase activity[134]. In a phase I study of patients with advanced solid tumors half of the patients receiving VX-680 have attained 'stable disease' pathological status (MTD: 64 mg/h)[135]. VX-680 has been further assessed in phase II clinical trials in patients with T315I mutant CML, Ph+ALL and non-small-cell lung cancer (NCT00405054 and NCT00290550). However, all the clinical trials of VX-680 had been terminated due to the off-target effect of QTc prolongation observed [136].

AMG-900

AMG 900 is an orally bioavailable, potent and selective inhibitor of Aurora-A, -B and -C (K_i values of 5, 4 and 1 nM, respectively)[137]. In contrast to paclitaxel and three well-characterized Aurora kinase inhibitors (AZD1152, VX-680, and PHA-739358), AMG-900 exhibits uniform potency across tumor cell lines, including the multidrug resistant (MDR) P-gp- and BCRP-expressing cell lines, as well as an AZD1152-resistant HCT116 variant cell line that carries a missense mutation in one allele of the Aurora-B gene (W221L). AMG-900 induces polyploidy in tumor cells and increases p53 and $p21^{Cip1}$ expression, consistent with the inhibition

of Aurora-B activity. AMG-900 also displays significant antitumor activity in a panel of human xenograft models (TGI: 50%-97%), including three the multidrug resistant models representing five distinct tumor types[137].

Another pre-clinical study has demonstrated that AMG-900 potentiates the activity of microtubule-targeting agents in human metastatic breast cancer models. Combining AMG-900 with ixabepilone results in the regression of paclitaxel resistant MDA-MB-231 (F11) breast carcinoma xenografts, and more than half of the tumors failed to regrow after the cessation of drug treatment[138].

AMG-900 exhibits acceptable pharmacokinetic (PK) properties in preclinical studies, with low-to-moderate clearance and a small volume of distribution. It also has a terminal elimination half-life ranging from 0.6 to 2.4 h, and adequate absorption with an oral bioavailability of 31% to 107%. AMG 900 is now undergoing a phase I clinical trials to evaluate safety, tolerability and PK in advanced solid tumors (NCT00858377). Another clinical study of AMG 900 for oral administration in adult subjects with acute leukemia and related disorders has been completed, and the results are yet to be announced (NCT01380756).

SNS-314

Developed by Sunesis Pharmaceuticals, CA, USA, SNS-314 is a potent and selective pan-Aurora kinase inhibitor (IC_{50} of 9, 31 and 3 nM against Aurora-A, -B and -C, respectively)[139]. Seven kinases, including Trk A/B, Flt4, Fms, Axl, c-Raf and DDR2, are also inhibited by SNS-314, with IC_{50}s within 100-fold of Aurora-A. This compound displays potent

activity and inhibits histone H3 phosphorylation at Ser10 and cellular proliferation of the HCT116 cell line at low concentrations (EC_{50} =13 nM). SNS-314 also inhibits the proliferation of a diverse panel of cancer cell lines with IC_{50} values of 1.8-23 nM, independent of Aurora-A or -B protein expression[140]. SNS-314 has also been evaluated against the anaplastic thyroid cancer-derived cell lines CAL-62, 8305C, 8505C and BHT-101[141] with high potency (IC_{50} values ranging from 2.6 to 26.6 nM).

SNS-314 exhibits significant *in vivo* antitumor activities in a number of pre-clinical xenograft models. For example, intermittent dosing (150 mg/kg) with SNS-314 results in 96% tumor growth inhibition (day 36) in an HCT116 mouse xenograft model. Treatment with SNS-314 (170 mg/kg) also results in significant repression of tumor activity (54-91%) in a number of tumour xenograft models, including five tumor types with six cancer cell lines: MDA-MB-231, PC-3, H129, Calu-6, A2780 and A375[140]. SNS-314 exhibits dosing flexibility *in vivo* as tumor growth is reduced under a variety of dosing schedules, including weekly, bi-weekly, and 5 days on/9 days off[140]. In addition, sequential administration of SNS-314 with conventional chemotherapeutic compounds, such as carboplatin, gemcitabine, 5-FU, daunomycin, and SN-38, produced additive anti-proliferative effects and synergistic efficacy when administered in combination with gemcitabine, docetaxel, or vincristine. *In vivo*, SNS-314 also potentiated the antitumor activity of docetaxel in xenografts[142]. A phase I clinical trial of SNS-314 for the treatment of patients with advanced solid tumors has been completed and the result is pending (NCT00519662).

PF-03814735

PF-03814735 is developed by Pfizer Inc., NY, USA. It is a novel, potent, orally bioavailable and reversible inhibitor of both Aurora-A and -B kinase activity (IC_{50} values of 0.8 and 5 nM, respectively)[143]. Besides Aurora kinases, PF-03814735 also prominently inhibits several other protein kinases, including Flt1, FAK, TrkA, Met and FGFR1 (IC_{50}=10, 22, 30, 100 and 100 nM, respectively). The cellular effects of PF-03814735 on Aurora-A and -B include reduced levels of phospho-Aurora-A (Thr 288 with IC_{50}~20 nM) and phosphohistone H3 (with IC_{50}~50 nM) in MDA-MB-231 breast cancer cells[143].

Mechanistically, this compound functions by inducing cytokinesis block and resulting in cell proliferation inhibition, mitotic catastrophe and polyploidy[143]. Oral administration of PF-03814735 (once-daily of ≥20 mg/kg for 10 days) to mice bearing HCT-116 xenografts has been shown to result in significant and dose-dependent tumor growth inhibition in mice (≥50% relative to vehicle-treated mice). This tumor growth inhibition is associated with reduced phosphorylated histone H3 levels. Significant single-agent antitumor efficacy has been observed in five additional xenograft tumor models of A2780 ovarian carcinoma, MDA-MB-231 breast carcinoma, colo-205 and SW620 colorectal carcinomas, and HL-60 acute promyelocytic leukemia[143].

Recent research has indicated that small cell lung cancer (SCLC) and, to a lesser extent, colon cancer cell lines are extremely sensitive to PF-03814735. The status of the *MYC* gene family and retinoblastoma pathway members significantly correlates with the efficacy of PF-03814735, whereas Aurora-A and -B expression are unexpectedly weak predictors of

response[144]. *In vivo* experiments with two small cell lung cancer (SCLC) xenograft models have confirmed the sensitivity of *MYC* gene-driven models to PF-03814735.

A phase I pharmacokinetic and pharmacodynamic study has demonstrated that PF-03814735 is generally well tolerated, with manageable toxicities[145].

CYC116

CYC116 is developed by Cyclacel Pharmaceuticals, Inc., Scotland, UK. This compound potently inhibits Aurora-A and -B kinases with high specificities (K_i values of 8.0 and 9.2 nM, respectively). It also inhibits VEGFR2 (K_i=44 nM) and CDKs (K_i~50 fold higher than that of VEGFR2), but it does not have significant effects toward other kinases, such as PKA, Akt/PKB, PKC, GSK-3 α/β, CK2, Plk1 and SAPK2A[146].

CYC116 has been demonstrated to inhibit the proliferation of the MV4-11 AML cell line with an IC_{50} value of 34 nM and suppress the growth of various solid tumor and leukemia cell lines. These growth inhibitory effects have been shown to correlate with Aurora-A/B inhibition[146].

CYC116 is orally bioavailable and possesses anticancer activity *in vivo*. For example, oral treatment with CYC116 (75 and 100 mg/kg) led to a delay (2.3- and 5.8-day, respectively) of tumor growth, respectively, in a NCI-H460 large cell lung cancer xenograft model[146]. The phase I clinical evaluation of this compound in patients with advanced solid tumors has been terminated (NCT00560716), but the reason is not disclose.

PHA-739358 (Danusertib)

PHA-739358, developed by Nerviano Medical Sciences, exhibits strong activity against Aurora-A, -B, and -C (IC_{50}=13, 79, and 61 nM, respectively) and it also possesses cross-reactivities with specific receptor tyrosine kinases, such as FGFR1, Abl, Ret and Trka (IC_{50}=47, 25, 31, and 31 nM)[147]. In HeLa cells, PHA-739358 (0.1 μM) inhibits both Aurora-A and -B. PHA-739358 also suppresses Abl, Ret, and Trk-A in cell lines in which these proteins are relevant for growth or survival. Furthermore, PHA-739358 also selectively inhibits the FGFR1 pathway but not the EGFR pathway in NIH-3T3 cells.

The anti-proliferative effect of PHA-739358 has been demonstrated in several tumor cell lines covering different cancer types, including colon, breast, prostate, lung, and ovarian cancers[136]. In most of the cell lines tested, treatment of PHA-739358 resulted in inducing polyploidy without a strong impact on the timing of mitosis, indicating that the dominant phenotype is related to Aurora-B inhibition. Because Aurora-A inhibition would rather result in a G2/M arrest. In p53 wild-type MEFs, PHA-739358 induces a 4N accumulation, and subsequently apoptosis, most likely through activation of the postmitotic G1 checkpoint. By contrast, after treatment with PHA-739358, p53-deficient MEFs cells do not arrest with a 4N DNA content but continue through additional rounds of DNA synthesis to become >8N. In addition, treatment with PHA-739358 lead to increased p53 protein levels and an associated increase in $p21^{Cip1}$ protein in HCT-116 cells[147]. Thus, the p53 status might contribute to the variations in sensitivity of different cell lines to PHA-739358 [147].

PHA-739358 has been also tested in chronic myeloid leukaemia (CML) cell lines and

primary cells derived from CML patients[148]. Anti-proliferative effects of PHA-739358 are observed in a broad panel of leukemic cell lines irrespective of their BCR-ABL mutational status. Moreover, PHA-739358 induced strong anti-proliferative effects in $CD34^+$ stem/progenitor cells derived from untreated CML patients (IC_{50}=0.005 μM) and from Imatinib-resistant individuals in chronic phase or blast crisis (IC_{50}=0.009 μM), including those harboring the T315I Imatinib-resistant mutation (IC_{50}=0.019 μM). PHA-739358 acts via the combined inhibition of BCR-ABL and Aurora kinases, as indicated by the significant decrease in the phosphorylation of both histone H3 and CrkL (a downstream target of BCR-ABL) upon treatment with PHA-739358. The activity of PHA-739358 against both Ph-positive and -negative ALL cells has recently been reported[149,150]. Furthermore, PHA-739358 also induces apoptosis and inhibits proliferation and migration in hepatocellular carcinoma and melanoma cells[151].

The antitumor activity of PHA-739358 *in vivo* has been evaluated in several human tumor xenograft models in nude mice as well as syngeneic rat models, such as transgenic and carcinogen-induced tumor models[147]. With a good safety profile, PHA-739358 treatment (60 mg/kg for 5 days or 30-45 mg/kg for 10 days) causes a significant tumor growth inhibition (TGI of 66% to 98%). The efficacy of this compound in rat models is similar to that observed in xenograft mouse models. For example, administration of PHA-739358 BID intravenously (i.v.; 25 mg/kg) to DMBA-induced primary mammary carcinomas rats resulted in tumor growth inhibition (TGI=75%), with complete regression in one animal. In an orthotopic xenograft model, PHA-739358 has also been observed to efficiently inhibit growth of liver metastases from gastroenteropancreatic neuroendocrine tumors[152]. Mechanistic studies in an A2780 mouse

xenograft model demonstrate that a decrease in phosphorylation level of histone H3-positive cells and an increase in p53- and $p21^{Cip1}$-positive cells are observed in tumors after treatment with PHA-739358, indicative of Aurora-kinase inhibition and cell cycle arrest.

PHA-739358 is one of the first Aurora kinase inhibitors to enter the clinic and has been studied in phase I and II trials. In one phase I study in patients with advanced or metastatic solid tumors, stable disease was observed in 24% of the evaluable patients; in five patients, disease stabilization was maintained for longer than 6 months. Biomarker analysis reveals inhibition of histone H3 phosphorylation in skin biopsies starting at a dose of 190 mg/m^2 [153]. In the other phase I study, PHA-739358 was well tolerated with target inhibition in the skin ($\geq$500 $mg/m^{2)}$ [154]. In an explorative study of patients treated in phase I and phase II trials, no relationships between PHA-739358 clearance and drug metabolizing enzymes and transporter protein ABCB1, ABCG2 polymorphisms were observed, although significantly higher clearance was observed in one patient with the FMO3 18281AA polymorphism[155]. However, PHA-739358 mono-therapy shows minimal efficacy in patients with castration-resistant prostate cancer in a randomized phase II study[69]. In agreement, a multi-tumor, multi-institutional phase II study of PHA-739358 showed that PHA-739358 alone only had marginal anti-tumor activity in common solid tumors after failure of prior systemic therapies[70]. Further studies are required to establish specific biomarkers predictive for either response or prolonged disease stabilization, as well as to design of combination therapeutic strategies. The preclinical and clinical experience with PHA-739358 has also been discussed by Meulenbeld HJ and colleagues[156].

AT9283

AT9283 was developed by Astex Pharmaceuticals via structure-based optimization of a ligand-efficient pyrazole-benzimidazole fragment. AT9283 inhibits Aurora-A, Aurora-B, JAK3, JAK2 and Abl (T315I) with IC_{50} values of 3, 3, 1.1, 1.2 and 4 nM, respectively[157].

The ability of AT9283 to inhibit the growth and survival of tumor cells as well as its *in vivo* antitumor activity have been demonstrated in multiple solid tumor and leukemia cell lines and human tumor xenograft models. For example, AT-9283 inhibits the growth and survival of HCT116 cells and produces the polyploid cellular phenotype typically associated with Aurora-B kinase inhibition[157]. It also suppresses colony formation by HCT116 cells (IC_{50}=30 nM). At 15 and 20 mg/kg for 16 days, AT9283 significantly inhibits tumor growth in an HCT116 xenograft mouse model (TGI=67% and 76%). AT9283 is also highly effective against B-non-Hodgkin lymphoma (B-NHL) cells *in vitro* and *in vivo*[158]. AT9283 induces apoptosis in a dose- and time-dependent manner and inhibits cell proliferation (IC_{50} of <1 μM), which are associated with the mechanism of action of Aurora-B inhibition.

Another preclinical study evaluates AT9283 against pediatric acute leukemia cells[159], and find that AT9283 significantly inhibits the growth and survival of cells derived from patients with pediatric leukemia. Specifically, AT9283 promotes Flt-3 dephosphorylation and inhibits the activity of downstream effectors, such as ERK and MEK. AT9283 also induces cell growth inhibition and apoptosis in MM cells[160]. A mechanism study reveals that AT9283 inhibits both Aurora-A and Aurora-B as well as STAT3 tyrosine phosphorylation. The combination of AT9283 with lenalidomide produces significant synergistic cytotoxicity in MM cells, which is associated

with increased inhibition of phosphorylated STAT3 and phosphorylated extracellular signal-regulated kinase. Inhibition of tumor growth is also observed in an MM cell xenograft mice model.

Moreover, AT9283 exhibits synergistic anticancer efficacy when combined with various novel and conventional agents (apicidin, 17-AAG and doxorubicin). At very low doses (5 nM), AT9283 in combination with docetaxel induce apoptosis more efficiently (23%) than AT9283 or docetaxel alone (10%). Consistent with this result, in a mouse xenograft model of mantle cell lymphoma, AT9283 (15 mg/kg) or docetaxel (10 mg/kg) alone has modest antitumor activity, whereas AT9283 (20 mg/kg) and AT9283 (15 or 20 mg/kg) plus docetaxel (10 mg/kg) exhibit significant tumor growth inhibition and enhanced survival.

Three phase I studies have been completed, and one is underway. In one phase I study, forty patients with advanced tumors were treated with AT9283 [161]. The result shows that AT9283 is generally well tolerated, and the dose-limiting toxicity of AT9283 is grade III febrile neutropenia in two patients 36 mg/m^2/72 h). The Maximum tolerated dose (MTD) of AT9283 was established at 27 mg/m^2/72 h, and the mean oral bioavailability of a 0.9 mg/m^2 dose was 29.4% (range 11.2%-36.7%).

3.13 Natural AKIs

Several natural compounds have been reported to inhibit Aurora kinase expression and activity in cancer cells.

Curcumin

Curcumin, an active compound present in turmeric and curry, has been demonstrated to potently inhibit Aurora-A promoter activity and mRNA expression in human bladder cancer T24 cells. Furthermore, Curcumin is also able to inhibit the phosphorylation of Aurora-A and histone H3. Curcumin treatment induces monopolar spindle, G2/M arrest, and a reduction in cell division. These phenomena can be attenuated by ectopic expression of Aurora-A[162]. Curcumin has also been shown to enhance chemosensitivity to anticancer drugs in breast cancer cells[163].

Tanshinones I

Tanshinones I is an extract from the Chinese herb *Salvia miltiorrhiza* and it exhibits potent effects on growth inhibition of breast cancer cells, consistent with Aurora-A downregulation[164,165]. *In vivo* studies have revealed that tanshinones I inhibits the growth of H1299 lung tumor in a dose-dependent manner and significantly inhibits lung tumor angiogenesis. Epigenetic mechanism studies also uncover that the tanshinones I treatment reduces the acetylation levels of histone H3 associated with Aurora-A gene.

Withanone

Withanone is an herbal ligand derived from roots of *Withania somnifera.* It has been identified by a computational approach through docking studies and is selected to bind to the TPX2-Aurora-A complex. The association of withanone with the complex results in the dissociation of TPX2 from the Aurora-A. In addition, withanone treatment also causes the disruption of the mitotic spindle apparatus in cancer cells. As Aurora-A is functionally regulated

by its interactions with TPX2, withanone provides a strategy to alter Aurora-A kinase signaling in an ATP-independent manner via targeting of the TPX2-Aurora-A complex[166].

3.2 Drug resistance and sensitivity to AKIs

Although many targeted anticancer drugs have now been clinically validated as effective cancer therapies, primary and acquired resistance to such treatments often arises and is becoming major obstacles to successful cancer therapy. Recent research has focused on identifying mechanisms and developing more effective strategies to predict and overcome drug resistance.

The crystallographic analysis and biochemical methods have used to design and validate the Aurora-A mutant T217D as a drug-resistance target for the Aurora-A kinase inhibitors MLN8054 and MLN8237[167].

As p53 is regulated by Aurora kinase-dependent phosphorylation, and the p53-dependent post-mitotic checkpoint is also important for preventing genome reduplication after mitotic defect. Hence, p53 in turn predicts sensitivities for inhibition of the Aurora kinases. For example, the loss of p53 in cancer cells has been shown to sensitize cells to anti-cancer drugs targeting both Aurora-A and -B (MLN8237, MK-5108, ZM447439, and Barasertib)[168]. Another report shows that triple-negative breast cancer cells with a mutation in p53 and increased p53 expression are more sensitive than other breast cancer cell lines to ENMD-2076, another Aurora-A inhibitior[169]. Consistently, the induction of apoptosis in response to MLN8237 exposure is dependent on the activity of p53 family [170]. In addition, the latelet-activating factor acetylhydrolase and GTP-binding nuclear protein Ran contribute to the development of

resistance to Aurora-A/B inhibitor ZM447439 related to p53 in HCT116 colon cancer cells[171]. On the other hand, a p53-independent mechanism of resistance related to autophagy has been found to another Aurora-A/B inhibitor, CYC116.

The Aurora-A binding protein TPX2 also predicts sensitivity for Aurora-A inhibition. Appropriately, the sensitivity of non-Hodgkin lymphoma (NHL) cell lines to a novel Aurora-A-specific inhibitor, MK-8745, correlates with the expression level of the Aurora-A activator TPX2[172].

3.3 Combination therapy

3.31 AKIs combined with conventional chemo- and radio- therapies

AKIs have shown great potential for enhancing the efficacy of chemotherapies and radiotherapies for multiple types of cancer. Taxanes are widely used in chemotherapy, but many patients are intrinsically or will become resistant to taxane-based treatments. Functional mitotic checkpoints are essential for taxane sensitivity, and amplification of Aurora-A overrides the mitotic spindle assembly checkpoint, conferring resistance to taxanes. Inhibition of Aurora-A or its substrates TACC3 and CENP-A, significantly increases the sensitivity to paclitaxel in cancer cells [173,174]. Consistent with this observation, the Aurora-A inhibitor CYC3 in combination with paclitaxel can lead to synergistic cytotoxicity in pancreatic cancer cells[175]. In addition, the combination of the Aurora-A inhibitor MLN8237 and docetaxel results in a higher level of cell death and reduction of tumor growth in preclinical cell models of upper gastrointestinal adenocarcinomas and mantle cell lymphoma[176,177]. Mahadevan D *et al*. also report that

MLN8237 combined with docetaxel or vincristine plus rituximab can culminate in synergistic curative efficacy in aggressive B-cell non-Hodgkin lymphoma[178]. Another study demonstrates that the ubiquitin (Ub)-specific processing protease-7 (USP7) interacts and cooperates with protein death domain-associated protein (Daxx) in the regulation of mitosis and taxane resistance, while inhibition of Aurora-A attenuates USP7-mediated taxane resistance[179].

Through a FOXO-dependent mechanism, the Aurora-A inhibitor MLN8237 can significantly potentiate the anti-leukemic activity of ara-C in both AML cell lines and primary blasts *in vitro* and augment the efficacy of ara-C without affecting its pharmacokinetic profile *in vivo*[61]. In addition, the Aurora-A inhibitor MLN8237 enhances cisplatin-induced cell death in esophageal adenocarcinoma cells[180].

3.32 AKIs combined with other targeted therapeutics

The combination of AKIs with other targeted drugs has also yielded promising efficacy and represents a novel therapeutic strategy for cancer treatment. HDAC inhibitors that interfere with HDAC activity have recently been investigated as promising drugs for targeted cancer therapies. AKIs have been shown to decrease the activity of HDAC proteins, and recent research has explored whether the combination of AKIs and HDAC inhibitors will achieve additive or synergistic effects in cancer cells. For example, co-treatment with Aurora-A/B kinases inhibitors VX-680 (MK-0457) and vorinostat (also known as suberanilohydroxamic acid or SAHA) leads to synergistic anti-cancer activity against human breast cancer cells *in vitro*, as well as greater tumor growth inhibition and better survival of mice bearing MDA-MB-231 xenografts[181].

Moreover, vorinostat can induce both transcriptional and post-transcriptional changes to create a pro-apoptotic milieu that sensitizes lymphoma cells to AKIs[182].

Imatinib, one of the first cancer-targeted drugs, has produced encouraging results in the treatment of multiple cancers, most notably Ph+CML. However, resistance to Imatinib mediated by mutations in the BCR-ABL domain has become a major problem in the treatment of these patients. The HDAC inhibitors vorinostat and/or pracinostat (SB939) in combination with VX-680 has synergistic inhibitory effects on the proliferation of BCR-ABL mutant (T315I) cells[183].

Concomitant inhibition of mTOR and Aurora-A kinase by Rapamycin and MLN8237 can also combine to abrogate the proliferation of uterine leiomyosarcoma cells only when MLN8237 is pre-administered[184]. Furthermore, we have demonstrated that in AML cells, the Aurora-A/B kinases inhibitor VX-680 induces polyploid cells with increased glycolytic metabolism rather than cell death. Inhibition of the mTOR pathway by mTOR inhibitors (rapamycin or PP242) or 2DG or the knockdown of p62, sensitizes these cells to AKIs[185].

In addition, the Aurora-A inhibitor MK-5108 increases the efficacy of an anti-GD2 ganglioside (GD2) 14G2a antibody in cultures of human neuroblastoma cells, correlating with a reduction of N-Myc as well as an induction of PHLDA1 and p53 proteins[186]. In a synthetic lethal screen study, Aurora-A inhibitor has been shown to be able to synergize with EGFR antagonists to reduce cell viability and tumor size[187].

NEDD9 is an activator of Aurora-A and confers Aurora-A stability. Combination therapy with NEDD9 shRNAs and Aurora-A inhibitors impairs tumor growth and distant metastasis in

mice harboring breast tumor xenografts[188]. Interestingly, NEDD9 serves as a scaffolding protein of both Aurora-A and SRC. As expected, the combination of Aurora kinase and SRC inhibitor demonstrates potent synergy in ovarian and colorectal cancer cell lines, indicating a potential strategy for targeted cancer therapy[189].

4. FUTURE DIRECTIONS

Oncogenic functions of Aurora-A are involved in the processes of proliferation, survival, invasion and stemness, which lie the basis for targeted therapy. However, Aurora-A is also critical for the cell proliferation at physiological conditions, and the mechanisms that distinguish its oncogenic function from the physiological one remain to be illustrated. Further improvements in Aurora kinase targeting are needed for tailoring treatment that selectively and effectively target cancer in individual patients.

Numerous AKIs have been developed, yet none is approved for clinical application. Indeed, most of AKIs exhibit distinct effect against cancer cells, but fail in preclinical or clinical evaluations[190]. High toxicity lies the prime obstacle for the applications of AKIs. Indeed, a number of toxicities are associated with Aurora-B inhibition[191]. Recent efforts in targeting Aurora-A by its selective inhibitor MLN8237 yield encouraging results[125,192]. Actually, a closer look at the history of AKIs development reveals that the road to success (length of effectiveness in evaluations) is associated with Aurora-A selectivity. Therefore, evidence from years of efforts indicate that selectively targeting Aurora-A may lead to the road to successful AKIs.

In addition to the optimizing the chemical structures of AKIs to increase their specificity and

reduce toxicity, the efficacy of AKIs could be improved by using these agents in combination with conventional chemo- or radio-therapies, or other targeted agents. First, conventional anticancer therapies generally kill both cancer and normal cells. The combination of AKIs and chemo- or radio-therapies could have benefit of reducing drug doses, thus causes decreased adverse effects. Second, conventional chemo- or radio-therapies kill cancer cells by inducing DNA damages, which subsequently activate cell cycle checkpoints and triggers apoptosis. While overexpression of Aurora kinases induces dysfunction of cell cycle checkpoints, leads to resistance to apoptosis. Thus, AKIs could help to reduce the resistance to chemo- or radio-therapies induced by Aurora kinase overexpression. Accumulating preclinical data have demonstrated synergistic effects between AKIs and other therapeutic strategies. Additional clinical studies are needed to evaluate the safety and efficacy of such combinations.

The well accepted idea of personalized cancer therapy also applies to successful Aurora-A targeting therapy. Specifically, biomarkers for selecting AKI responsive patients that benefit from Aurora-A targeting therapy need to be developed. To improve the precision of evaluation, biomarker driven clinical studies should be applied. Currently, biomarkers including mitotic index, chromosome alignment, spindle bipolarity and activated Aurora-A have been used to assess the efficacy of Aurora inhibition in patients. In addition, p53 status, TPX2 expression, MYCN expression, and chromosome numbers, predict sensitivity to AKIs. However, biomarkers that consistently distinguish AKI sensitive and resistant population, is yet to be defined. Indeed, biomarkers are not only indicators of sensitivity (screening biomarker), but also candidates for improving efficiency and overcoming resistance (therapeutic biomarker). Thus, both screening

and therapeutic biomarkers need to be defined before the successful application of Aurora-A targeted therapy.

Furthermore, emerging evidence suggests that the translocation of oncogenic proteins lead to distinct functions in tumorigenesis. For example, nuclear epidermal growth factor receptor (EGFR) functions as a transcription factor[193]. Our identification of nuclear specific trans-activating activity in promoting cancer stemness opens a new field of spatially deregulated Aurora kinases in the nucleus[83]. The inhibitors capable of blocking nuclear translocation of Aurora-A will have potential anti-cancer efficacy (Fig.5). Further studies on the mechanisms of nuclear translocation and nuclear specific functions will prompt the process of targeting oncogenic Aurora-A.

Finally, kinase activity of Aurora-A, a candidate therapeutic target, is essential for a plenty of oncogenic processes. Current strategies against oncogenic Aurora-A are restricted to its kinase activity, overlooking the kinase-independent oncogenic functions. However, kinase-independent activity, which bypass kinase inhibition should be underscored. Indeed, kinase-independent functions of Aurora-A have been demonstrated in both physiological and malignant contexts. Notably, a promising AKI MLN8237 suppresses kinase-independent function of Aurora-A (N-Myc interaction)[88,90], suggesting a rationale for fully targeting oncogenic Aurora-A. Indeed, a growing number of evidence demonstrates non-canonical activity of oncogenic kinases (eg. CDK6[194], LKB1[195] and PKM2[196]), indicating that kinase independent oncogenic activity may be important for therapeutic resistance. This evidence indicates that in addition to inhibition of kinase activity, elucidating and targeting kinase-independent oncogenic activity acts as a wiser

strategy for targeting oncogenic kinases (Fig.6).

ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (973 Program, 2012CB967000 and 2011CB504300 to Q. Liu), National Natural Science Foundation of China (81130040 to Q. Liu, 81201547 to M. Yan and 81402445 to C.L. Wang), Program for Innovative Research Team in University (IRT13049 to Q. Liu), the National High Technology Research and Development Program of China (863 Program, 2015AA020926 to Z.J. Long), and the Liaoning (NSF2014029102 to Q. Liu).

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Figure and Table legends

Figure 1 Structures and expression patterns of Aurora kinases.

(A) Domain Organization of Aurora kinases. The catalytic domain of Aurora-A, -B and -C is highly conserved (green region). Autophosphorylation of Thr288 in the activation loop of Aurora-A is required for the activation of its kinase activity. A short amino acid peptide motif known as the 'destruction box' (D-box) is present in the carboxy-terminal region of Aurora-A, -B and -C. The D-box is recognized by adaptors of the anaphase-promoting complex/cyclosome and thereby targets those proteins for degradation through the ubiquitin/proteasome-dependent pathway. Aurora-A and Aurora-B have the amino terminal "D-box-activating domain box (A-Box)" required for the functional activation of D-box.

The expression levels and localization of Aurora-A and -B kinases in cell cycle are indicated in (B) and (C) respectively. In G1 phase, the level of Aurora-A is rarely detectable. During S phase, a small proportion of Aurora-A is first detected at centrosomes. At late G2 phase, Aurora-A accumulates evidently at centrosomes and becomes activated [3]. During prometaphase and metaphase, active Aurora-A localizes on bipolar spindles and spindle poles after nuclear-envelope breakdown (NEBD). At the metaphase-anaphase transition, majority of Aurora-A is inactivated and degraded. A small fraction of Aurora-A remains on the centrosomes and the spindles at the onset of anaphase, and localizes to the spindle midzone and centrosomes during late anaphase and telophase/cytokinesis [2,4].

In mammalian cells, Aurora-B is first found on pericentromeric heterochromatin during late S phase, and keep active throughout mitosis with protein level peaking in G2/M phase[197]. In

prophase Aurora-B targets to heterochromatin, and further enriches at the inner centromeres during prometaphase before the metaphase-to-anaphase transition. At the onset of anaphase Aurora-B relocates to spindle microtubules and then to the equatorial cell cortex during cytokinesis[198-201].

Figure 2 Aurora-A functions as an oncogene through regulating multiple molecular targets and signaling pathways.

Aurora-A contributes to cancer development associating with inducing genomic instability, enhancing proliferation, survival, migration and invasion of cancer cells, as well as promoting cancer stem cell phenotype.

Figure 3 Interaction between Aurora-A and p53.

Phosphorylation (Ser315) of p53 by Aurora-A induces MDM2-mediated destabilization of p53[84]. In addition, Aurora-A phosphorylates p53 at Ser215, leading to abrogation of p53 DNA binding and transactivation activity[85]. In p53 deficient cells, CDK2 is activated by reducing $p21^{Cip1}$ expression, resulting in pRb hyperphosphorylation and its dissociation from transcriptional factor E2F3. E2F3 then bind to the *AURKA* gene promoter and transactivate, Aurora-A expression. Deficiency in p53 also causes the downregulation of Fbw7α, a component of E3 ligase that targets of Aurora-A for degradation[86]. Moreover, p53 suppresses the oncogenic activity of Aurora-A *via* direct interaction with the latter's Aurora box [87]. A red line indicates promotion, while a blue one represents suppression.

Figure 4 Interaction between Aurora-A and Myc.

Aurora-A forms a complex with the oncogenic N-Myc protein, which protects N-Myc from

proteasomal degradation mediated by the Fbxw7 ubiquitin ligase[88]. Moreover, Aurora-A-mediated stabilization of N-Myc up-regulates VEGF expression and promotes angiogenesis[89]. The Aurora-A inhibitors MLN8054 and MLN8237 disrupt this Aurora-A/N-Myc complex and promotes N-Myc degradation[90]. LIN28B coordinates Ran and Aurora-A to promote MYCN expression [94]. In addition, nuclear Aurora-A forms a complex with hnRNPK on *MYC* promoter, which activate *MYC* transcription[83]. Conversely, c-Myc regulates Aurora-A expression by directly inducing its transcription [96]. The Myc transcription factor and its Max binding partner are associated with *AURKA* promoter during the G2 phase of the cell cycle[97]. A red line indicates promotion, while a blue one represents suppression.

Figure 5 Targeting Aurora-A for nuclear translocation.

In normal cells, Aurora-A localizes in cytoplasm, while in cancer cells, Aurora-A expresses in both cytoplasm and nucleus. The nuclear Aurora-A also has oncogenic functions (eg. transactivation of c-Myc and promotion of CSCs), blocking the nuclear translocation of Aurora-A could have potential anti-cancer efficacy. ANLIs, Aurora-A nuclear location inhibitors.

Figure 6 Targeting Aurora-A for both kinase-dependent and -independent functions.

As Aurora-A functions as an oncogene through both kinase-dependent and -independent mechanisms, the combination of Aurora-A kinase inhibitors (AKIs) and Aurora-A kinase independent inhibitors (AKIIs) could be a more effective therapeutic strategy.

Table 1. Overexpression, amplification or polymorphisms of Aurora kinases in various cancer types.

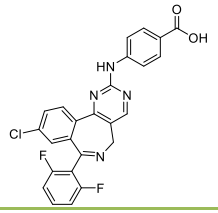
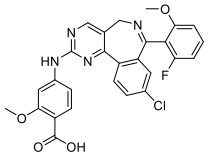
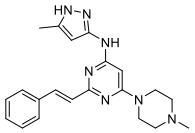
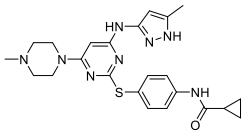
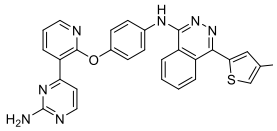
Table 2. Aurora kinase inhibitors in clinical trials.

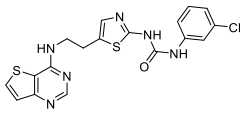
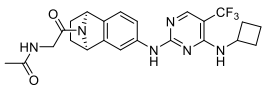
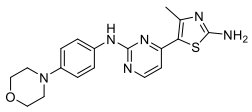
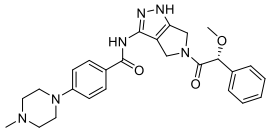
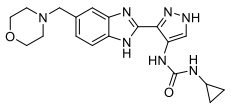
Table 1 Overexpression, amplification or polymorphisms of Aurora kinases in various cancer types.

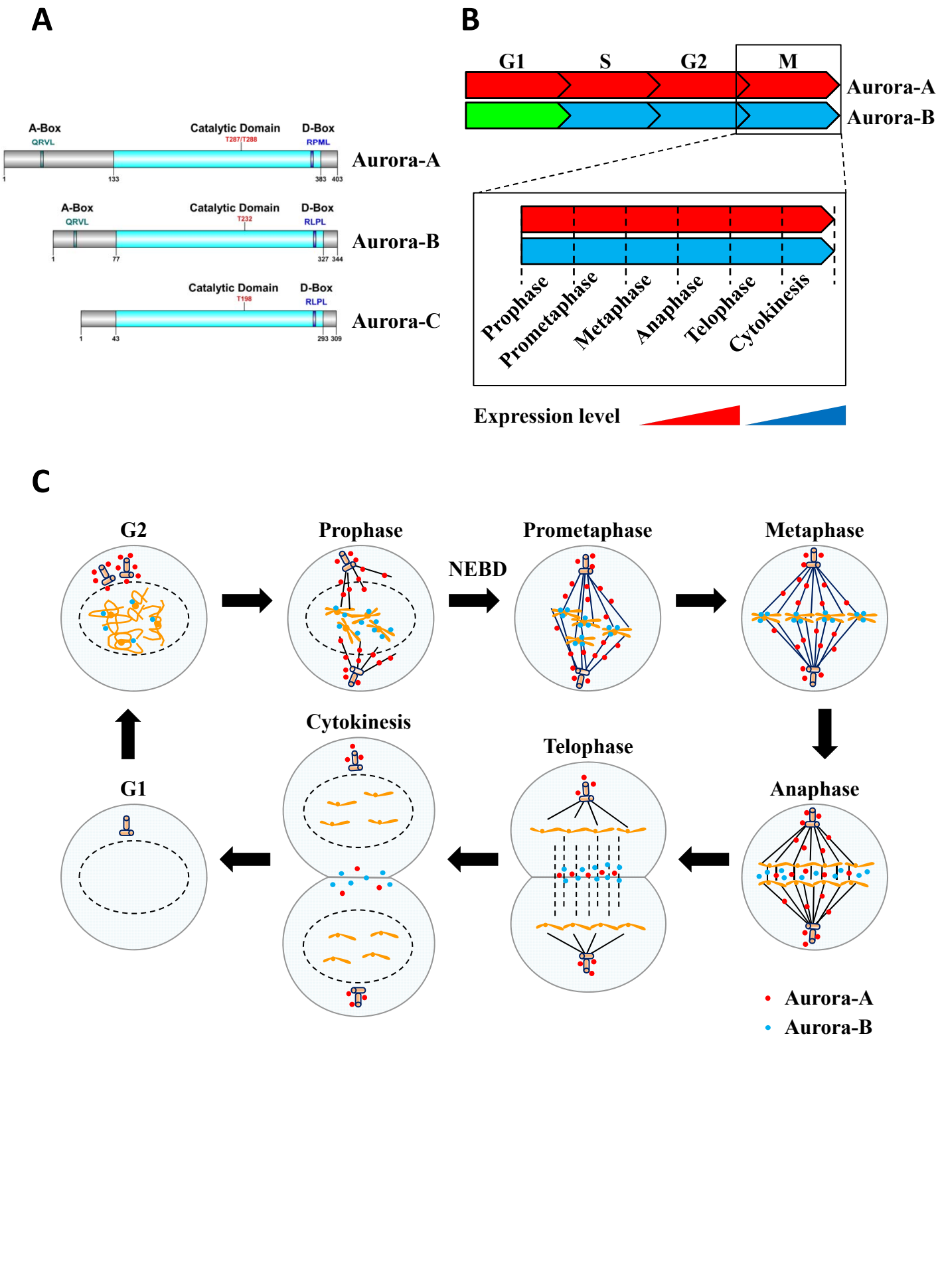
Aurora kinase	Tumor type	Correlation of clinical relevant information	Ref.
Aurora-A	Breast cancer	nuclear grade, lymph node status, Ki-67, p53, EMT markers, estrogen, progesterone and HER-2/neu receptor, basal-like tumor phenotype, RFS	64,100,103,202-209
	Gliomas	tumor grade, survival	210,211
	Ovarian cancer	p53, tumor grade, proliferation index, aneuploidy, stage, DFS	203,212,213
	Prostate cancer	RFS, tumor grade	100,203,214,215
	Cervical cancer	FIGO stage, tumor differentiation, parametrial invasion, lymphnode, hematogenous metastasis, DFS and OS	203,216,217
	Lung cancer	chemotherapeutic resistance, OS and DFS	218-221
	Head and neck carcinoma	tumor stage, regional lymph node, distant metastasis, DFS and OS	65,66,104,222,223
	Gastric tumor	survival	224,225
	Esophageal carcinoma	cancer risk, invasive malignancy, metastatic disease, tumor recurrence, DFS, MTS, chemoratiotherapy-resistance	106,226-230
Aurora-B	Oral cancer	Ki-67, histological differentiation, tumor stage and size, lymph node metastasis, metastasis and DFS	231,232
	Breast cancer	p53, proliferation index, histological grade, lymph node metastasis, chemoresistance, survival	233,234
	Non-small cell lung cacinoma	sex, age, aneuploidy, tumor differentiation, histological type, tumor size, lymph node metastasis, vascular invasion, shorter survival for the patients with adenocarcinoma histology	235-237
	Glioma	survival	238
Aurora-C	Colorectal cancer	tumor grade	239

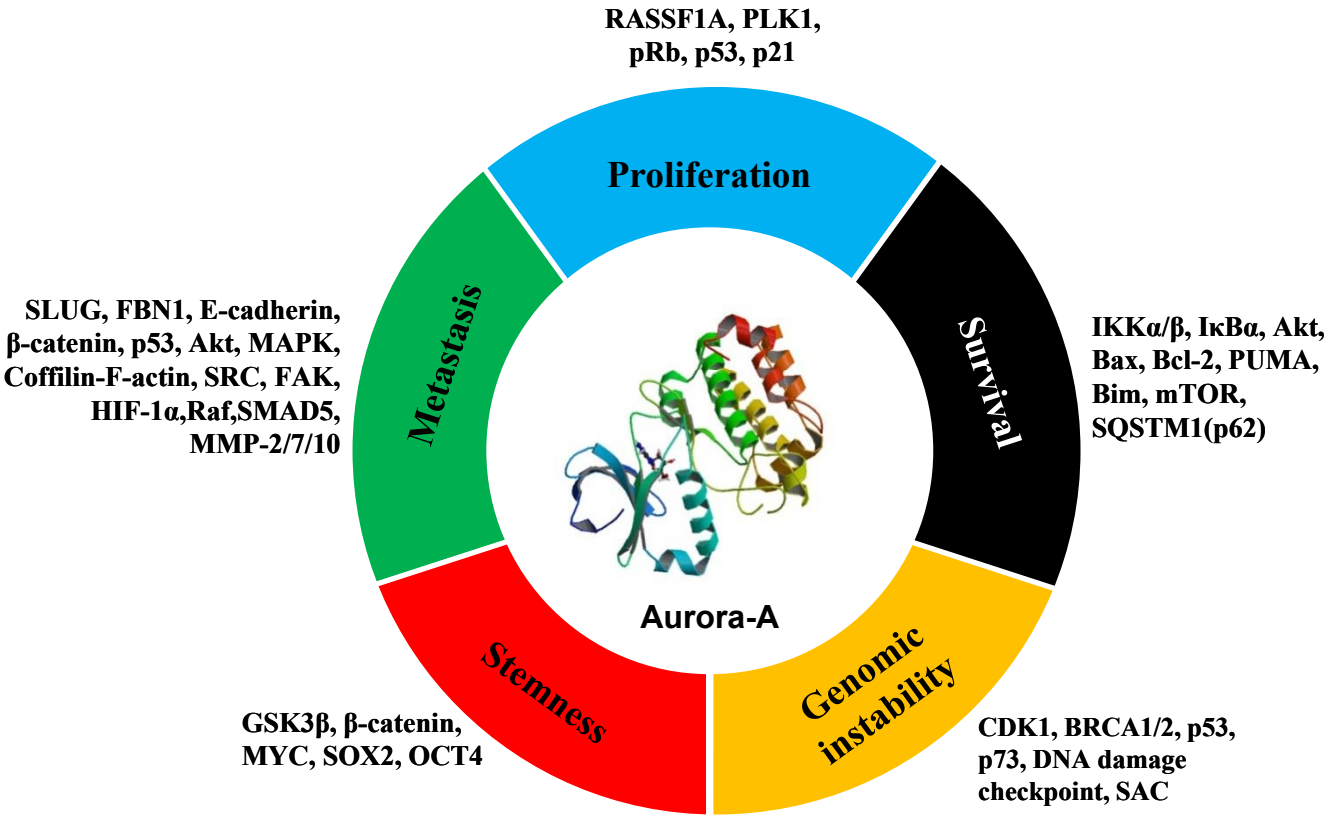
RFS: relapse-free survival; DFS: disease-free survival; FIGO: International Federation of Gynecology and Obstetrics; OS: overall survival; MTS: median survival time

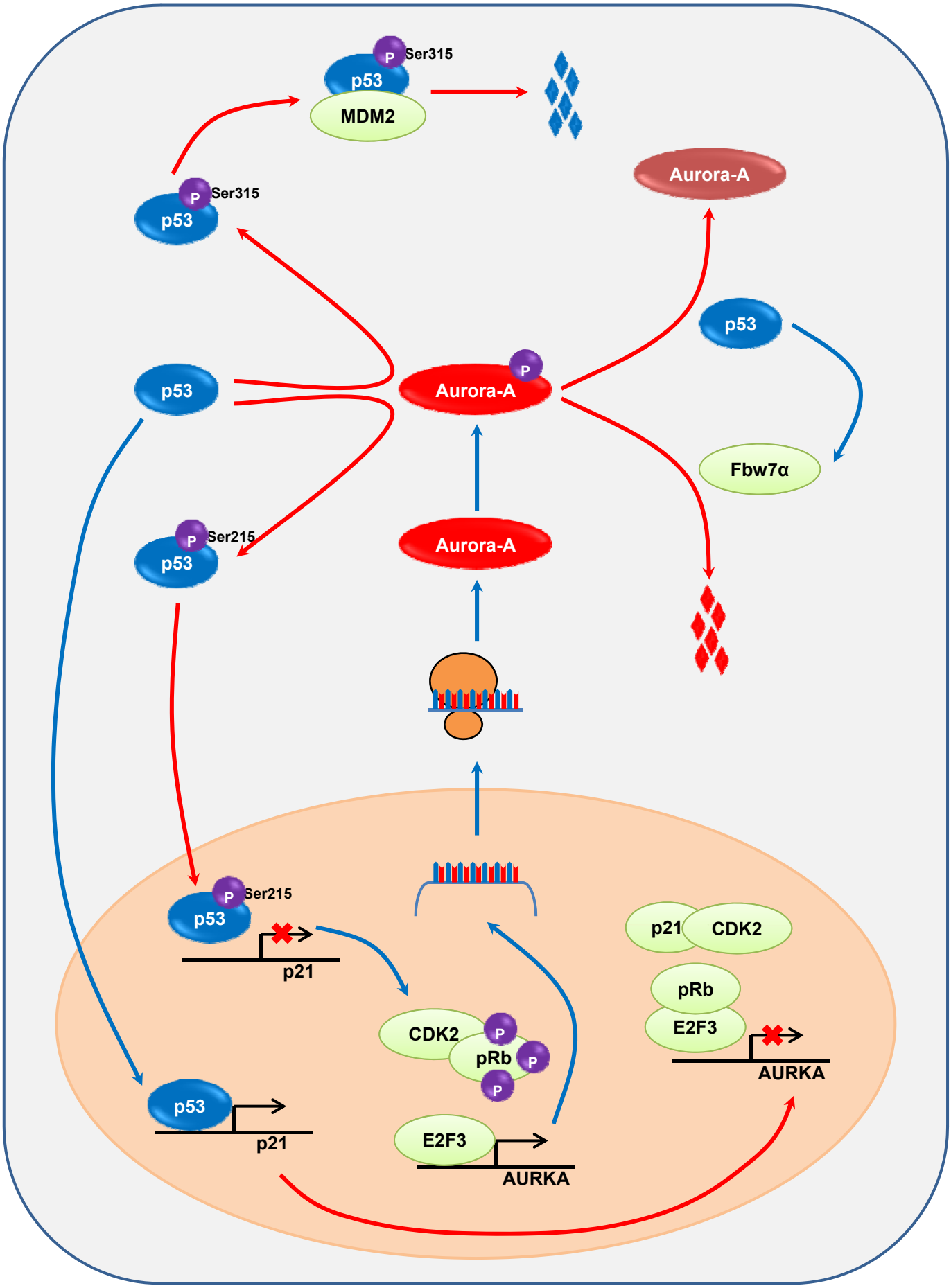
Table 2 Aurora kinase inhibitors in clinical trials.

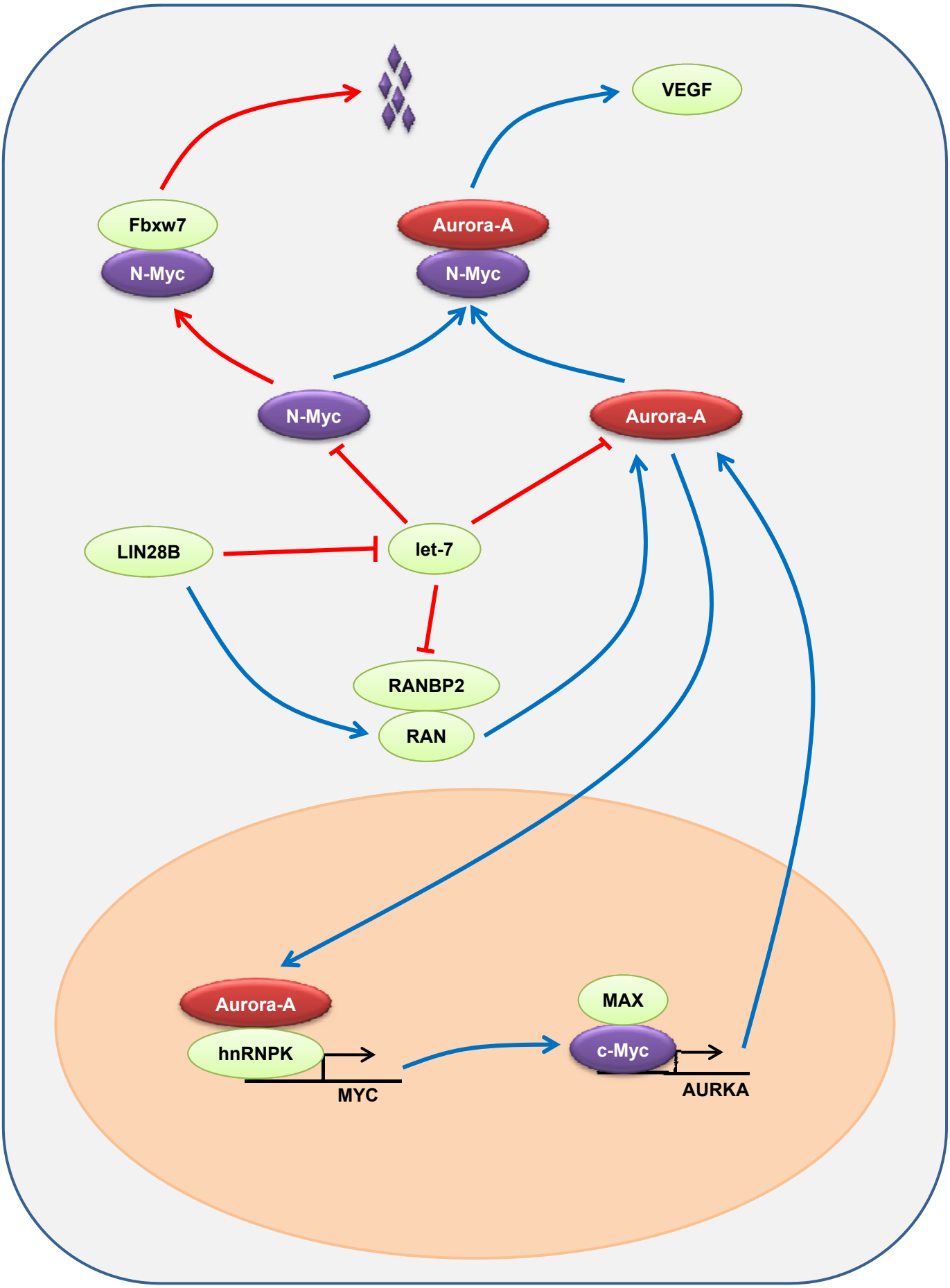
Inhibitor	Structure	Company	Target	Administration	Types of tumors	Status	Ref.
MLN8054		Millennium	Aurora-A IC_{50} 4 nM	Oral	Advanced solid tumors	Phase I	36,109,110
MLN8237 (Alisertib)		Millennium	Aurora-A IC_{50} 1.2 nM	Oral	Advanced solid tumors, leukemia, lymphoma	Phase I/II	113,116
					Relapsed/refractory peripheral T-cell lymphoma	Phase III	
ENMD-2076		EntreMed	Aurora-A IC_{50} 14 nM	Oral	Relapsed or refractory hematological malignancies, multiple myeloma	Phase I	126,129
					Ovarian cancer, triple negative breast cancer, advanced fibrolamellar carcinoma	Phase II	
VX-680 (MK-0457)		Vertex/ Merck	Aurora-A Ki 0.6 nM Aurora-B Ki 18 nM Aurora-C Ki 4.6 nM	I.V.	Solid tumors, leukemia	Phase I/II	58,131,132
AMG900		Amgen	Aurora-A IC_{50} 5 nM Aurora-B IC_{50} 4 nM Aurora-C IC_{50} 1 nM	Oral	Advanced solid tumors, leukemia	Phase I	137,240

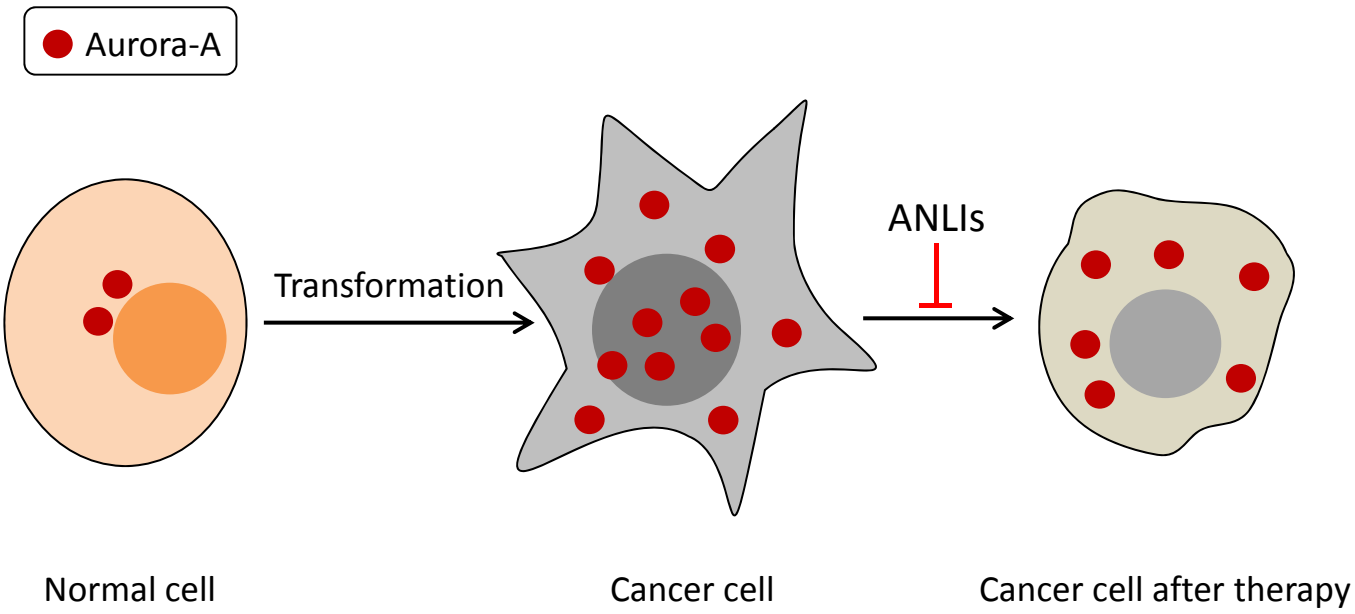
SNS-314		Sunesis	Aurora-A IC_{50} 9 nM Aurora-B IC_{50} 31 nM Aurora-C IC_{50} 3 nM	I.V.	Advanced solid tumors	Phase I	139,142
PF-03814735		Pfizer	Aurora-A IC_{50} 0.8 nM Aurora-B IC_{50} 5 nM	Oral	Advanced solid tumors	Phase I	143
CYC116		Cyclacel	Aurora-A Ki 8 nM Aurora-B Ki 9.2 nM	Oral	Advanced solid tumors	Phase I	146
PHA-739358 (Danusertib)		Nerviano	Aurora-A IC_{50} 13 nM Aurora-B IC_{50} 79 nM Aurora-C IC_{50} 61 nM	I.V.	Metastatic hormone refractory prostate cancer, multiple myeloma	Phase II	147
AT9283		Astex	Aurora-A IC_{50} 3 nM Aurora-B IC_{50} 3 nM	I.V.	Advanced solid tumors, leukemia, lymphoma	Phase I/II	157

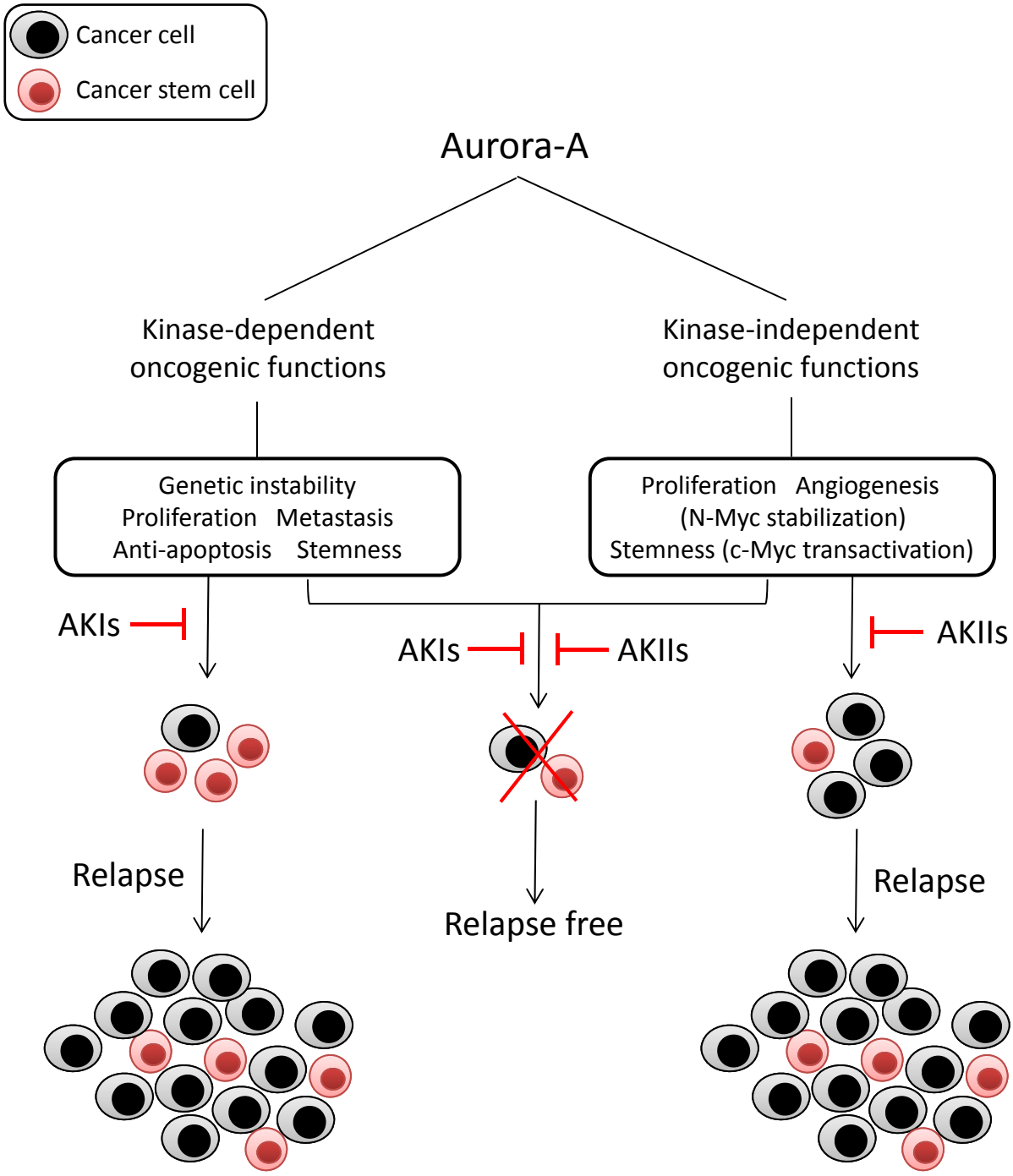

A
A-Box
QRVL
Catalytic Domain
T287/T288
D-Box
RPML
Aurora-A
1
133
383
403
A-Box
QRVL
Catalytic Domain
T232
D-Box
RLPL
Aurora-B
1
77
327
344
Catalytic Domain
T198
D-Box
RLPL
Aurora-C
1
43
293
309
B
G1
S
G2
M
Aurora-A
Aurora-B
Prophase
Prometaphase
Metaphase
Anaphase
Telophase
Cytokinesis
Expression level
C
G2
Prophase
NEBD
Prometaphase
Metaphase
Anaphase
Telophase
Cytokinesis
G1
Aurora-A
Aurora-B


RASSF1A, PLK1,
pRb, p53, p21
Proliferation
Survival
IKKα/β, IκBα, Akt,
Bax, Bcl-2, PUMA,
Bim, mTOR,
SQSTM1(p62)
Genomic
instability
CDK1, BRCA1/2, p53,
p73, DNA damage
checkpoint, SAC
Stemness
GSK3β, β-catenin,
MYC, SOX2, OCT4
Metastasis
SLUG, FBN1, E-cadherin,
β-catenin, p53, Akt, MAPK,
Coffilin-F-actin, SRC, FAK,
HIF-1α,Raf,SMAD5,
MMP-2/7/10
Aurora-A


P
Ser315
p53
MDM2
Aurora-A
P
Ser315
p53
p53
Aurora-A
P
p53
Fbw7α
P
Ser215
p53
Aurora-A
P
Ser215
p53
p21
p21
CDK2
pRb
E2F3
AURKA
CDK2
P
pRb
P
P
p53
p21
E2F3
AURKA


VEGF
Fbxw7
N-Myc
Aurora-A
N-Myc
N-Myc
Aurora-A
LIN28B
let-7
RANBP2
RAN
Aurora-A
hnRNPK
MYC
MAX
c-Myc
AURKA


Aurora-A
Transformation
ANLIs
Normal cell
Cancer cell
Cancer cell after therapy


Cancer cell
Cancer stem cell
Aurora-A
Kinase-dependent oncogenic functions
Kinase-independent oncogenic functions
Genetic instability
Proliferation Metastasis
Anti-apoptosis Stemness
Proliferation Angiogenesis
(N-Myc stabilization)
Stemness (c-Myc transactivation)
AKIs
AKIs
AKIIs
AKIIs
Relapse
Relapse free
Relapse