

Aurora Kinases: New Targets for Cancer Therapy

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Abstract The Aurora kinase family is a collection of highly related serine/threonine kinases that functions as a key regulator of mitosis. In mammalian cells, Aurora has evolved into three related kinases known as Aurora-A, Aurora-B, and Aurora-C. These kinases are overexpressed in a number of human cancers, and transfection studies have established Aurora-A as a bone fide oncogene. Because Aurora overexpression is associated with malignancy, these kinases have been targeted for cancer therapy. This article reviews the multiple functions of Aurora kinase in the regulation of mitosis and the mitotic checkpoint, the role of abnormal Aurora kinase activity in the development of cancer, the putative mechanisms of Aurora kinase inhibition and its antitumor effects, the development of the first generation of Aurora kinase inhibitors, and prospects for the future of Aurora kinase inhibition in the treatment of cancer.

The Aurora kinase family is a collection of highly related serine/threonine kinases that are key regulators of mitosis, essential for accurate and equal segregation of genomic material from parent to daughter cells. These kinases are involved in multiple facets of mitosis and cell division, including centrosome duplication, mitotic spindle formation, chromosome alignment upon the spindle, mitotic checkpoint activation, and cytokinesis. Errors in these processes ultimately lead to aneuploidy or cell death.

Aurora kinases have been conserved throughout eukaryotic evolution and, in mammalian cells, have evolved into three related kinases known as Aurora-A, Aurora-B, and Aurora-C. Despite significant sequence homology, the localization and functions of these kinases are largely distinct from one another. Aurora-A localizes to the centrosome from centrosome duplication through mitotic exit and primarily functions in centrosome regulation and mitotic spindle formation. Aurora-B is a subunit of the chromosomal passenger protein complex and functions to ensure accurate chromosome segregation and cytokinesis. Aurora-B undergoes dynamic localization during mitosis, localizing first to the inner centromeric region from prophase through metaphase and then to the spindle midzone and midbody from anaphase through cytokinesis. Aurora-C is also a chromosomal passenger protein and colocalizes with Aurora-B. Unlike Aurora-B, Aurora-C is specifically expressed in the testis where it functions in spermatogenesis and regulation of cilia and flagella. Although expression of Aurora-C is seen in

some transformed cells, its role in cancer development currently is unclear and will not be further discussed in this review.

Dysregulation of Aurora has been linked to tumorigenesis. *Aurora-A* is located on chromosome 20q13.2, a region commonly amplified in malignancies, such as melanoma and cancers of the breast, colon, pancreas, ovaries, bladder, liver, and stomach. Interest in Aurora has intensified since the discovery that transfection of rodent Rat1 and NIH3T3 fibroblast cell lines with *Aurora-A* is sufficient to induce colony formation in culture and tumors in nude mice, thus establishing *Aurora-A* as a bone fide oncogene (1, 2).

Aurora-B is located on chromosome 17p13.1, a region not typically amplified in human malignancies. Despite lack of amplification at the gene level, mRNA and protein levels of *Aurora-B* are frequently increased in tumors, such as colorectal cancer (3). Although *Aurora-B* has not been established as an oncogene by standard criteria, exogenous overexpression of *Aurora-B* in Chinese hamster embryo cells results in subsequent chromosome separation defects during mitosis and increased invasiveness *in vivo*, suggesting a role for *Aurora-B* in tumorigenesis (4).

Given the association of Aurora overexpression and tumorigenesis, these kinases have been targeted for cancer therapy, and a new class of drugs known as Aurora kinase inhibitors has been developed. Four small-molecule inhibitors of Aurora [Hesperadin (5); ZM447439 (6); MK0457, previously VX-680 (7); and PHA-680632 (8)] have shown antitumor properties in published preclinical studies. Clinical trials of MK0457 and three other Aurora kinase inhibitors (MLN8054, AZD1152, and PHA-739358) are ongoing in the United States and Europe.

Aurora Function and Regulation

Aurora-A. *Aurora-A* is ubiquitously expressed and regulates cell cycle events occurring from late S phase through M phase, including centrosome maturation (9), mitotic entry (10, 11), centrosome separation (12), bipolar-spindle assembly (13, 14), chromosome alignment on the metaphase plate (12, 15), cytokinesis (12), and mitotic exit (Table 1). *Aurora-A*

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Received 6/12/06; revised 8/28/06; accepted 9/12/06.

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doi:10.1158/1078-0432.CCR-06-1405

Table 1. Localization and function of human Aurora kinases

Phase	Localization	Function	Putative substrates
Aurora-A			
G ₁	Undetectable	NA	TACC, centrosomin, SPD-2, XMAP215, γ TuRC, Ajuba, Eg5, Ran-TPX2, CENP-A, PP1, p53, CDH1, NM23-H1, CPEB
Late S phase	Duplicated centrosomes	Centrosome maturation	
G ₂	Duplicated centrosomes	Mitotic entry	
Prophase	Duplicated centrosomes	Centrosome separation	
Prometaphase	Spindle poles	Bipolar-spindle assembly	
Metaphase	Spindle poles	Chromosome alignment on the metaphase plate	
Anaphase	Spindle midzone/centrosomes	Cytokinesis	
Telophase	Spindle midzone/centrosomes	Cytokinesis	
Aurora-B			
G ₁	Undetectable	NA	INCEP, survivin, Borealin, MCAK, BubR1, Mad2, CHO1/MKLP-1/ZEN4, myosin II regulatory light chain, vimentin, desmin, Histone H3, CENP-A, REC-8, RACGAP1, GF AP, CPEB
G ₂	Undetectable	NA	
Prophase	Nucleus	Recruitment of centromeric proteins	
Prometaphase	Kinetochores	Recruitment of centromeric proteins Chromosome biorientation and segregation	
Metaphase	Kinetochores	Mitotic checkpoint	
Anaphase	Spindle midzone	Cytokinesis	
Telophase	Spindle midzone/ Cleavage-furrow	Cytokinesis	

Abbreviation: NA, not available.

protein levels and kinase activity both increase from late G₂ through M phase, with peak activity in prometaphase. During G₂, Aurora-A interacts with the LIM protein Ajuba, resulting in autophosphorylation of Aurora-A in its activating T-loop (10). Following mitotic entry, further activation of Aurora-A is mediated by the Ran-TPX2 (targeting protein for XLKP2, a *Xenopus* kinesin-like protein) pathway (Fig. 1; ref. 16). TPX2, a spindle protein that is both substrate and activator of Aurora-A (13, 14), induces Aurora-A autophosphorylation and protects it from the inhibitory action of the type 1 protein phosphatase 1 γ .

Once activated, Aurora-A mediates its multiple functions by interacting with various substrates including centrosomin, transforming acidic coiled-coil protein, cdc25b, Eg5, and centromere protein A. Recently described substrates include p53 (17), MBD3 (18), a potential activator of histone deacetylase 1, and BRCA1 (19), all of which may be important mediators in malignant transformation. Following mitotic exit, a conserved destruction box (D-box) sequence in the COOH-terminal region of Aurora is recognized by the anaphase-promoting complex/Fizzy-related, thus mediating degradation of Aurora-A via the ubiquitin/proteasome-dependent pathway (20, 21).

The role of Aurora-A, both in normal cellular physiology and tumorigenesis, has been comprehensively reviewed by Marumoto et al. (22), and the reader is referred to this article for further information on this topic.

Aurora-B. Aurora-B is a chromosomal passenger protein critical for accurate chromosomal segregation, cytokinesis (5, 6, 23, 24), protein localization to the centromere and kinetochore, correct microtubule-kinetochore attachments (25), and regulation of the mitotic checkpoint. Aurora-B localizes first to the chromosomes during prophase and then to the inner centromere region between sister chromatids during prometaphase and metaphase (Table 1; ref. 26). During prometaphase, Aurora-B is responsible for the correct localization and stabilization of centromeric proteins, including Borealin, the inner centromeric protein (INCENP), and survivin (27). Aurora-B is activated by both INCENP and survivin, with peak activity in metaphase and telophase (28). Key substrates of activated Aurora-B include the centromeric proteins centromere protein A, INCENP, survivin, Borealin; microtubule-destabilizing kinesin mitotic centromere-associated kinesin; the mitotic checkpoint proteins BubR1 and Mad2; the cytoskeletal proteins myosin II regulatory light chain, vimentin, desmin, and glial fibrillary acidic protein; and histone H3. Histone H3 is a protein involved in chromosome condensation and mitotic entry, and its phosphorylation on Ser¹⁰ is mediated by Aurora-B (29). Following mitosis, the D-box region of Aurora-B is recognized by the anaphase-promoting complex/cyclosome, leading to Aurora-B ubiquitination and degradation (30).

Aurora-B participates in the establishment of chromosomal biorientation, a condition where sister kinetochores are linked to opposite poles of the bipolar spindle via amphitelic

attachments (Fig. 2). Proper biorientation is necessary for accurate chromosome alignment and segregation. Errors in this process, manifesting as a merotelic attachment state (one kinetochore attached to microtubules from both poles) or a syntelic attachment state (both sister kinetochores attached to microtubules from the same pole), lead to chromosomal instability and aneuploidy if not corrected before the onset of anaphase. The primary role of Aurora-B at this point of mitosis is to repair incorrect microtubule-kinetochore attachments (5, 6, 31). When proper amphitelic attachment occurs, tension is created at the centromere by the microtubule-kinetochore attachment and is counteracted by centromeric cohesion.

If either a merotelic or syntelic attachment occurs, Aurora-B senses the lack of tension at the centromere and severs the microtubule-kinetochore attachment (5, 6, 32). The resulting unattached kinetochore then generates a "wait anaphase" signal, thereby activating the mitotic checkpoint (6). This checkpoint (reviewed in ref. 33) is a complex surveillance mechanism that senses microtubule defects or aberrant kinetochore attachments and is the primary mechanism of cell cycle control in mitosis (5, 6). It is a signaling cascade that prevents progression of a cell from metaphase to anaphase when even a single chromosome is not properly attached to the mitotic spindle. Aurora-B plays an essential role in this checkpoint by recruiting several checkpoint proteins, including BubR1 and Mad2, to unattached kinetochores, and maintaining inhibition of the anaphase-promoting complex/cyclosome, an E3 ubiquitin ligase essential for mitotic progression (34). Without Aurora-B activity, the mitotic checkpoint is compromised, resulting in increased numbers of aneuploid cells, genetic instability, and tumorigenesis (reviewed in ref. 35).

Aurora-A Overexpression and Tumorigenesis

Aurora-A overexpression is a necessary feature of Aurora-A-induced tumorigenesis; however, both abnormal cellular

localization and timing of Aurora-A expression are also implicated. In normal cells, Aurora-A is expressed primarily during the G₂-M phase transition and is located at the centrosomes and mitotic spindle; in malignant cells, Aurora-A is detected diffusely throughout the cell, regardless of cell cycle position (36). This suggests that, in malignancy, Aurora-A is aberrantly active during G₁ and S phase and is active in cellular areas other than the centrosomes and spindle. It may thus be both over-phosphorylation of normal Aurora-A substrates and aberrant phosphorylation of cytoplasmic targets and targets present during the G₁ and S phases of the cell cycle that ultimately lead to malignant transformation.

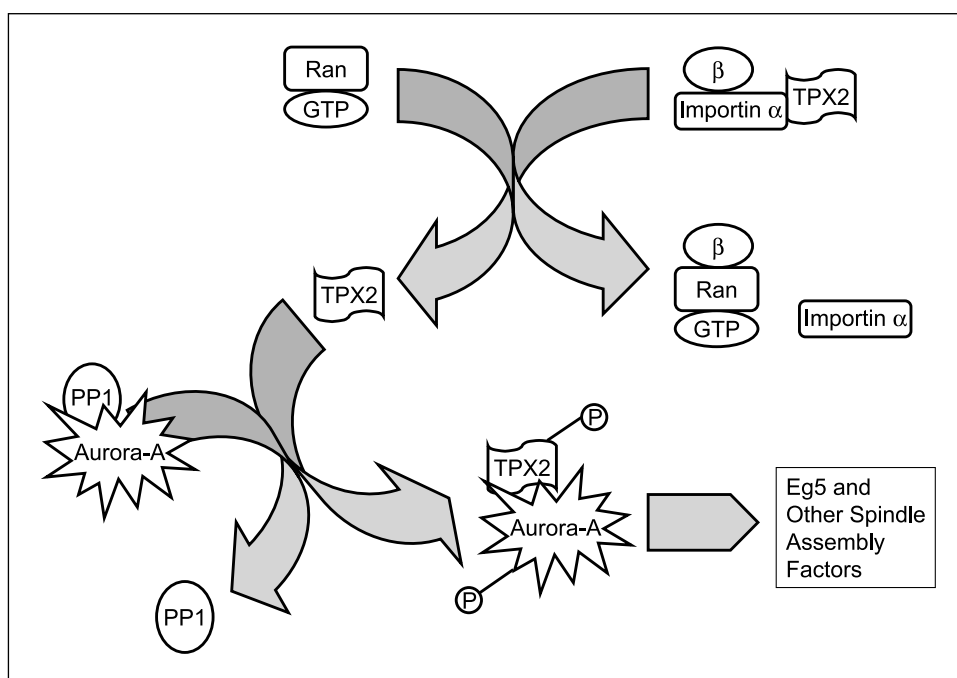
In cells with Aurora-A overexpression, mitosis is characterized by the presence of multiple centrosomes and multipolar spindles (1, 2, 37). Despite the resulting aberrant microtubule-kinetochore attachments, cells abrogate the mitotic checkpoint and progress from metaphase to anaphase, resulting in numerous chromosomal separation defects. These cells fail to undergo cytokinesis, and, with additional cell cycles, polyploidy and progressive chromosomal instability develop (37, 38).

Development of Aurora Kinase Inhibitors

The evidence linking Aurora overexpression and malignancy has stimulated interest in developing Aurora inhibitors for cancer therapy. In normal cells, Aurora-A inhibition results in delayed, but not blocked, mitotic entry (10, 12); centrosome separation defects resulting in unipolar mitotic spindles (12, 39); and failure of cytokinesis (12). Encouraging antitumor effects with Aurora-A inhibition were shown in three human pancreatic cancer cell lines (Panc-1, MIA PaCa-2, and SU.86.86), with growth suppression in cell culture and near-total abrogation of tumorigenicity in mouse xenografts (40).

Aurora-B inhibition results in abnormal kinetochore-microtubule attachments, failure to achieve chromosomal

Fig. 1. Aurora-A activation. Formation of the bipolar spindle requires activation of Aurora-A by the targeting protein for XKLP2 (TPX2). TPX2, which exists in an inhibitory complex with importin- α/β at the onset of mitosis, is released by Ran-GTP and is then free to bind to Aurora-A. TPX2 interferes with the inhibitory activity of protein phosphatase 1 γ (PP1 γ) upon Aurora-A and enables Aurora-A to autophosphorylate, thereby activating itself and other substrates, including TPX2. Activated Aurora-A then recruits spindle assembly factors, such as Eg5, that are necessary for the formation of the bipolar spindle.



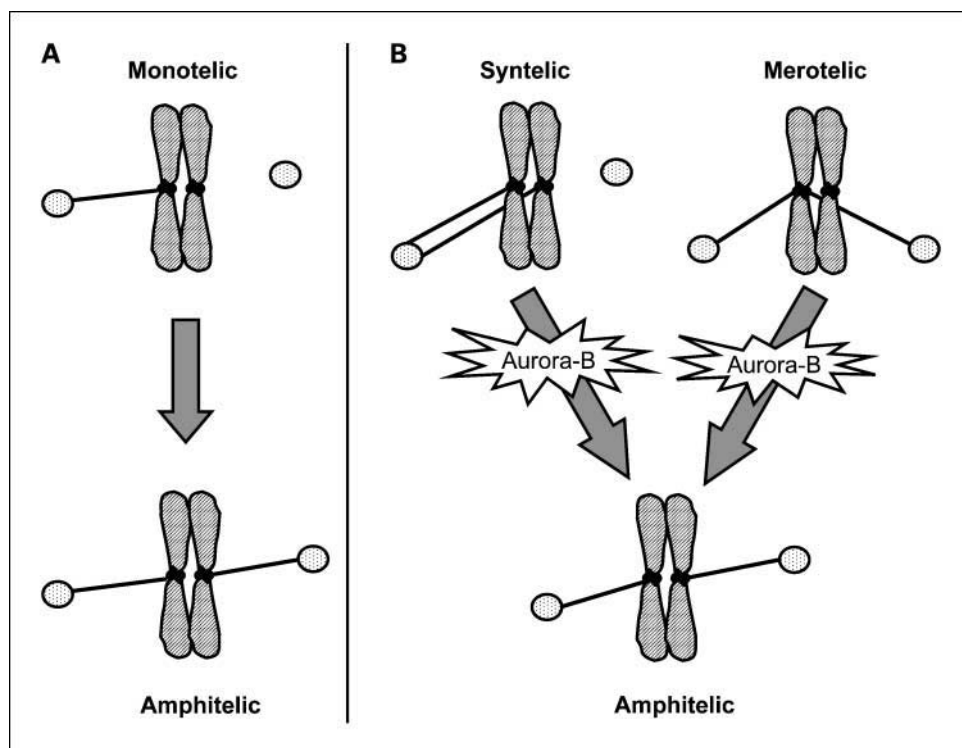


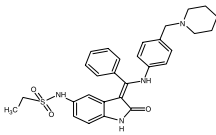
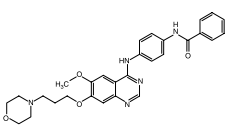
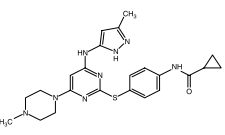
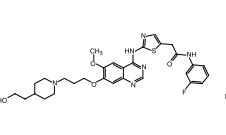
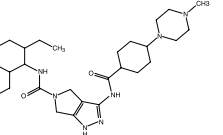
Fig. 2. Aurora-B and the establishment of chromosome biorientation. *A*, in most cases, the initial kinetochore-microtubule attachment is a monotelic attachment where only one kinetochore (*black*) is attached to one pole of the spindle (*dotted circle*). A second kinetochore-microtubule attachment then occurs between the sister chromatid and the opposite spindle pole, thus producing a correct amphitelic attachment state. *B*, incorrect attachments can occur if both kinetochores establish microtubule connections to the same pole (syntelic attachment) or if one kinetochore is attached to both poles (merotelic attachment). Aurora-B senses the unequal tension across the kinetochore pairs caused by these aberrant attachment modes and decreases the stability of the syntelic and merotelic attachments. In this manner, the generation of the amphitelic attachment state necessary for proper chromosome segregation is promoted.

biorientation, and failure of cytokinesis (24, 41). The mitotic checkpoint is compromised, allowing cells to progress through mitosis despite incorrect microtubule-kinetochore attachments (5, 42). Although the initial recruitment of checkpoint proteins, such as BubR1 and Mad2, to kinetochores occurs normally during prophase, they subsequently dissociate as mitosis progresses in the absence of Aurora-B function. This dissociation weakens the checkpoint, allowing cells undergoing abnormal mitosis to progress from metaphase to anaphase. Recurrent

cycles of aberrant mitosis without cytokinesis result in massive polyploidy and, ultimately, to apoptosis (5, 6, 23, 25, 42).

Inhibition of Aurora-A or Aurora-B activity in tumor cells results in impaired chromosome alignment, abrogation of the mitotic checkpoint, polyploidy, and subsequent cell death. These *in vitro* effects are greater in transformed cells than in either non-transformed or non-dividing cells (6). Thus, targeting Aurora may achieve *in vivo* selectivity for cancer. Although toxicity to rapidly dividing cell of the hematopoietic

Table 2. Aurora kinase inhibitors

	Hesperadin (Boehringer Ingelheim)	ZM447439 (AstraZeneca)	MK0457 (Merck)	AZD1152 (AstraZeneca)	PHA-680632 (Nerviano Medical Sciences)
Chemical class	Indolinone	Quinazoline derivative	4,6 Diaminopyrimidine	Quinazoline derivative	Tetrahydropyrrolo [3,4-c] pyrazole derivative
Aurora-A IC ₅₀	NA	110 nmol/L	0.6 nmol/L	687 nmol/L	27 nmol/L
Aurora-B IC ₅₀	50 nmol/L in cells; >200 μmol/L <i>in vitro</i>	130 nmol/L	18 nmol/L	3.7 nmol/L	135 nmol/L
Aurora-C IC ₅₀	NA	NA	4.6 nmol/L	17 nmol/L	120 nmol/L
Other targets	NA	MEK (1.79 μmol/L), SRC (1.03 μmol/L), LCK (0.88 μmol/L)	FLT3 (30 nmol/L)	NA	FGFR1 (0.4 μmol/L)
Structure					
Abbreviation: NA, not available.					

and gastrointestinal system is expected, the activity and clinical tolerability shown in xenograft models indicates the presence of a reasonable therapeutic index.

Given the preclinical antitumor activity and potential for tumor selectivity, several Aurora kinase inhibitors have been developed. The first three small-molecule inhibitors of Aurora described include ZM447439 (6), Hesperadin (5), and MK0457 (Table 2; ref. 7). The following agents are nonspecific inhibitors: ZM447439 inhibits Aurora-A and Aurora-B; Hesperadin inhibits primarily Aurora-B; MK0457 inhibits all three Aurora kinases. Each induces a similar phenotype in cell-based assays, characterized by inhibition of phosphorylation of histone H3 on Ser¹⁰, inhibition of cytokinesis, and the development of polyploidy (5–7). Selective inhibitors of Aurora have also been developed, including MLN8054, a selective Aurora-A inhibitor and Compound 677 and AZD1152, both selective Aurora-B inhibitors. The next generation of Aurora inhibitors is currently being developed, including agents by Nerviano Medical Sciences (PHA-680632 and PHA-739358), Rigel (R763), Sunesis (SNS-314), NCE Discovery Ltd. (NCED#17), Astex Therapeutics (AT9283), and Montigen Pharmaceuticals (MP-235 and MP-529). Several of these agents are undergoing evaluation in clinical trials (Table 3).

Hesperadin. Hesperadin is a novel indolinone that inhibits immunoprecipitated Aurora-B with an inhibitory concentration 50% (IC₅₀) of 250 nmol/L. It induces aberrant microtubule-kinetochore attachments, with a significant increase in the formation of syntelic attachments (5). Despite failing to achieve proper chromosome biorientation, treated cells evade the mitotic checkpoint and proceed from metaphase to anaphase (5, 7). These cells fail to undergo cytokinesis and tetraploidy results. Despite the increased polyploidy, no loss of cell viability is achieved.

MK0457. MK0457, initially developed by Vertex and now being developed clinically by Merck & Co., Inc., is a 4,6-diaminopyrimidine that targets the ATP-binding site common to all Aurora kinases. It is thus a potent inhibitor of all three Aurora kinases, with inhibition constants (*K_i*) of 0.6, 18.0, and 4.6 nmol/L for Aurora-A, Aurora-B, and Aurora-C, respectively (7). MK0457 additionally inhibits the activity of Fms-related tyrosine kinase-3, which is frequently increased in patients with acute myelogenous leukemia, as well as imatinib- and BMS-354825-resistant ABL(T3511) kinase (43).

Treatment with MK0457 results in polyploidy and additionally inhibits the growth of several tumor types in cell culture, with the induction of apoptosis most prominent in leukemia,

lymphoma, and colorectal cell lines. Studies of MK0457 in rodent xenograft models of leukemia, colon cancer, and pancreatic cancer also show impressive antitumor activity. Treatment of human acute myelogenous leukemia (HL60) nude mice xenografts with MK0457 resulted in a 98% reduction in tumor volume when compared with controls (7). In a human colon cancer (HCT116) nude rat xenograft model, treatment with MK0457 resulted in tumor regression in four of the seven rats treated. In all treated xenografts, phosphorylation of histone H3 at Ser¹⁰ was inhibited, indicating effective Aurora-B inhibition. Importantly, the centrosome separation defect characteristic of Aurora-A inhibition was not seen, suggesting a greater inhibition of Aurora-B by MK0457. The only significant toxicity noted in these studies was neutropenia, with count recovery occurring after the cessation of treatment. No effect was noted in non-cycling human cells.

Based on these encouraging preclinical data, Merck & Co. is sponsoring several clinical trials of MK0457 (Table 3), including two phase I trials in patients with advanced cancer, one phase I trial in patients with relapsed or refractory leukemia, and one phase II trial in patients with advanced non-small cell lung cancer. Preliminary data from 22 patients enrolled in an ongoing phase I trial of MK0457 given as a 5-day continuous infusion every 28 days reveals a maximum tolerated dose of 10 mg/m²/h (44). Neutropenia was the dose-limiting toxicity, with no significant anemia or thrombocytopenia observed. Unlike other antimetabolic agents, such as the taxanes, MK0457 was not associated with significant neuropathy. One patient with pancreas cancer and another with non-small cell lung cancer achieved prolonged stable disease lasting >6 months.

MLN8054. MLN8054 is an oral small-molecule inhibitor of Aurora with relative specificity for Aurora-A (Aurora-A IC₅₀ = 0.034 μmol/L; Aurora-B IC₅₀ = 5.7 μmol/L; ref. 45). Treatment of cultured human tumor cells with low concentrations of MLN8054 (0.25–2 μmol/L) results in aberrant mitotic spindle formation consistent with Aurora-A inhibition. Treatment at higher concentrations (4 μmol/L) results in loss of phosphorylation of histone H3 on Ser¹⁰, consistent with Aurora-B inhibition. Growth inhibition was shown in HCT116 human colon cancer, PC4 prostate cancer, and Calu-6 human lung cancer xenograft models using various oral dosing schedules (46). MLN8054 is currently being evaluated in a phase I trial for patients with advanced solid tumors (Table 3).

ZM447439, Compound 677, and AZD1152. ZM447439 is a quinazoline derivative developed by AstraZeneca that is an ATP competitor of Aurora. *In vitro* assays show inhibition of both

Table 3. Aurora kinases in current clinical trials

Agent	Targets	ClinicalTrials.gov identifier	Sponsor	Patient population
MK0457	Pan Aurora kinase inhibition	NCT00099346	Merck & Co.	Advanced cancer
	Pan Aurora kinase inhibition	NCT00104351	Merck & Co.	Advanced cancer
	FLT3 inhibition	NCT00104351	Merck & Co.	Relapsed or refractory leukemia
	Pan Aurora kinase inhibition	NCT00290550	Merck & Co.	Advanced non-small cell lung cancer
MLN8054	Aurora-A inhibition	NCT00249301	Millennium Pharmaceuticals	Advanced solid tumors
AZD1152	Aurora-B inhibition	NCT00338182	AstraZeneca	Advanced solid tumors
PHA-739358	Pan Aurora kinase inhibition	NCT00335868	Nerviano Medical Sciences	Relapsed chronic myelogenous leukemia

Aurora-A and Aurora-B with an IC₅₀ of ~100 nmol/L. As with Hesperadin, ZM447439 induces incorrect microtubule-kinetochore attachments, failure of chromosome biorientation, abrogation of the mitotic checkpoint, failure of cytokinesis, and the development of tetraploidy (5, 7). Treated cells either undergo apoptosis with the next cell cycle, where the inherited tetraploid genome and four centrosomes result in mitotic catastrophe, or a G₁ arrest, possibly induced by a p53-dependent G₁ tetraploidy checkpoint. Unlike with Hesperadin, exposure to ZM447439 achieves both growth inhibition and apoptosis. Interestingly, although ZM447439 inhibits both Aurora-A and Aurora-B *in vitro*, the phenotype observed in treated cells suggests a greater inhibition of Aurora-B. Specifically, neither the centrosome separation defect nor delayed mitotic entry characteristic of Aurora-A inhibition is seen (5–7).

Because the antitumor activity of both ZM447439 and MK0457 is ascribed primarily to Aurora-B inhibition, the development of selective Aurora-B inhibitors has been pursued. Compound 677, a selective Aurora-B inhibitor developed by AstraZeneca, shows potent single-agent anticancer activity in preclinical studies (47). Combinations of Compound 677 with various chemotherapeutic agents show enhanced antiproliferative effects. Although polyploidy was induced with treatment in all cells regardless of p53 or p21 status, preclinical data suggest that the presence of a nonfunctional p53 results in increased sensitivity to Compound 677 (47). Similarly, increased sensitivity to MK0457 has recently been associated with a compromised p53-p21 pathway and persistent Rb phosphorylation (48). The p53-p21 dependence of treatment efficacy may be a class effect of all Aurora inhibitors, providing further support for treatment selectivity towards transformed cells.

AZD1152 is another selective Aurora-B inhibitor developed by AstraZeneca. It is a highly soluble acetanilide-substituted pyrazole-aminoquinazolone pro-drug that is cleaved completely in human plasma to yield the active drug substance AZD1152 hydroxy-QPA. AZD1152 hydroxy-QPA inhibits Aurora-A, Aurora B-INCENP, and Aurora C-INCENP with respective inhibitory coefficients of 687, 3.7, and 17.0 nmol/L, indicating a 100-fold selectivity for Aurora-B over Aurora-A.

Cell line studies reveal inhibition of histone H3 phosphorylation at Ser¹⁰ and progression with normal kinetics through an aberrant mitosis, resulting in polyploidy and cell death.

Xenograft studies of AZD1152 show reduced phosphorylation of histone H3 on Ser¹⁰, increased polyploidy and enhanced apoptosis in athymic nude rodents bearing various human tumors, including colorectal cancer (SW620, HCT116, and Colo205) and lung cancer (A549 and Calu-6; ref. 49). When AZD1152 was dosed as a 48-hour continuous infusion, statistically significant, durable inhibition of tumor growth was observed in all xenograft models. Transient, reversible myelosuppression was the most significant adverse event observed.

Preliminary data from 19 patients enrolled in an on-going European phase I trial of AZD1152 given as a 2-hour weekly infusion reveals a maximum tolerated dose of 200 mg. As with MK0457, neutropenia was the dose-limiting toxicity. No significant anemia, thrombocytopenia, or neuropathy was observed. One patient with melanoma, one with nasopharyngeal carcinoma and one with adenocystic carcinoma achieved prolonged stable disease lasting >25 weeks (50). A phase I trial of this agent given as a 48-hour continuous infusion every 2 weeks and a 2-hour infusion given daily for 2 days every 2 weeks has recently opened in the United States.

Conclusion

Our understanding of the biological roles of Aurora-A and Aurora-B in both normal cells and malignancy has provided a platform for the rational development of a new class of targeted anticancer agents. Preclinical data for Aurora kinase inhibition is promising and preliminary clinical data reveals disease stability with treatment in an otherwise treatment-refractory patient population. Whether targeting Aurora-A, Aurora-B, or both will result in optimal antitumor activity is unknown. Results from on-going clinical trials evaluating pan-Aurora kinase inhibition (MK0457 and PHA-739358), selective Aurora-A inhibition (MLN8054), and selective Aurora-B inhibition (AZD1152) may answer this important question.

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Clin Cancer Res 2006;12:6869-6875.

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