Aurora Kinases as Anticancer Drug Targets

Oliver Gautschi,[1] Jim Heighway,[2] Philip C. Mack,[3] Phillip R. Purnell,[3] Primo N. Lara , Jr.,[3] and David R. Gandara[3]

Abstract The human aurora family of serine-threonine kinases comprises three members, which act in concert with many other proteins to control chromosome assembly and segregation during mitosis. Aurora dysfunction can cause aneuploidy, mitotic arrest, and cell death. Aurora kinases are strongly expressed in a broad range of cancer types. Aurora A expression in tumors is often associated with gene amplification, genetic instability, poor histologic differentiation, and poor prognosis. Aurora B is frequently expressed at high levels in a variety of tumors, often coincidently with aurora A, and expression level has also been associated with increased genetic instability and clinical outcome. Further, aurora kinase gene polymorphisms are associated with increased risk or early onset of cancer. The expression of aurora C in cancer is less well studied. In recent years, several small-molecule aurora kinase inhibitors have been developed that exhibit pre-clinical activity against a wide range of solid tumors. Preliminary clinical data from phase I trials have largely been consistent with cytostatic effects, with disease stabilization as the best response achieved in solid tumors. Objective responses have been noted in leukemia patients, although this might conceivably be due to inhibition of the Abl kinase. Current challenges include the optimization of drug administration, the identification of potential biomarkers of tumor sensitivity, and combination studies with cytotoxic drugs. Here, we summarize the most recent preclinical and clinical data and discuss new directions in the development of aurora kinase inhibitors as antineoplastic agents.

A defining characteristic of the malignant tumor cell is inappropriate growth. This aberrant behavior is accompanied by invasion into surrounding tissues and metastases to distant sites. The tumor cell phenotype is the consequence of a relatively high level of genetic instability, with sequential mutational and epimutational damage conferring growth and/or survival advantages to the tumor-initiating cell and its evolving progeny.

The mechanism of action of established and novel [reviewed in this issue (1–4)] cytotoxic chemotherapeutic agents essentially rests on the exploitation of tumor cell cycling to facilitate the preferential killing of tumor over normal host cells that are critical to survival. This selective killing may be achieved either by interfering with the synthesis/replication of DNA (e.g., using agents such as fluoropyrimidines, gemcitabine, or topoisomerase inhibitors), by the introduction of irresolvable lesions into the DNA of proliferating cells (e.g., platinum analogues and cyclophosphamide), or by disruption of the microtubule cytoskeleton essential for mitotic division (e.g., taxanes, *Vinca* alkaloids, and epothilones). Given that certain populations of normal and important cells also proliferate in adult tissues (e.g., in the bone marrow), it is not surprising that such cytotoxic agents are associated with some degree of severe normal tissue toxicity. Recent tumor genomics data, however, are now assisting in the development of more rationally selected drugs that target proteins expressed exclusively or at particularly high levels in tumor compared with essential normal adult cells. It is hoped that the specific pharmaceutical targeting of such proteins will result in a new generation of highly active drugs that are associated with minimal collateral host toxicity. We should also recognize, however, that given the underlying nature of the disease and the technology applied, many of the gene products so identified in analyses of expression in tumor versus normal tissue are likely to be intimately associated with the proliferative state and, further, that pharmacologic agents targeting such molecules may therefore again essentially represent a general targeting of proliferating cells. Tumor selectivity would in this case most likely rest on any indirect differential effects of removing target function in the tumor versus critical normal host cells (5). Indeed, proteins intimately involved in the regulation of the cell cycle (6), particularly cell cycle–associated kinases (7, 8), have been suggested as possible new anticancer targets.

Although the topic for this issue of *CCR Focus* is new cytotoxic compounds, the distinction between cytotoxic and cytostatic, and even between chemotherapy and targeted therapy, is perhaps of less importance and with perhaps less underlying biological rationale in 2008 than it was previously. In fact, targeted agents, such as epidermal growth factor

Authors' Affiliations: [1]Department of Medical Oncology, Bern University Hospital, Bern, Switzerland; [2]Cancer Communications and Consultancy Ltd., Cheshire, United Kingdom; and [3]University of California Davis Cancer Center, Sacramento, California

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Requests for reprints: David R. Gandara, University of California Davis Cancer Center, 4501 X Street, Suite 3016, Sacramento, CA 95817. Phone: 916-734-3772; Fax: 916-734-7946; E-mail: david.gandara@ucdmc.ucdavis.edu.

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receptor inhibitor or antiangiogenic tyrosine kinase inhibitors, do shrink tumors in some patients (i.e., a cytotoxic effect), whereas emerging data suggest that exploitation of the molecular targets of standard chemotherapy (e.g., using ERCC1 as a predictive biomarker for platinum compounds) is now an achievable goal in the clinic. In this review, we will consider the hypotheses that aberrant expression of two serine-threonine mitotic kinases, aurora A (encoded by *AURKA* on 20q13.2-13.31) and aurora B (encoded by *AURKB* on 17p13.1), contributes to the neoplastic phenotype; that aurora kinases are appropriate drug targets; and that inhibitors of these particular aurora kinases can add to the cancer therapeutic armamentarium, whether viewed as cytotoxic antineoplastics or as targeted agents capable of modulating the cytotoxicity of contemporary chemotherapy regimens.

Aurora Kinases

The aurora family comprises three related kinases that share the highest degree of sequence homology in their catalytic domains (9, 10). Expression of aurora A and B is closely linked to the proliferation of many, if not all, cell types, whereas for aurora C, the normal function of which is not clear, expression seems to be restricted to normal testicular tissue (11). Experimental data suggest that inappropriately high or low levels of aurora kinase activity are linked to genetic instability (12). Despite their sequence homology and common association with cycling cells, the subcellular distribution, partners, and substrates and therefore functions of aurora A and B are essentially nonoverlapping (Fig. 1; see refs. 8, 9, 12–14 for reviews).

Aurora A has well-established but perhaps not yet fully understood roles in centrosome function and duplication, mitotic entry, and bipolar spindle assembly. By the G_2 phase of the cell cycle through anaphase, it can be detected in the pericentriolar material. Additionally, it spreads to mitotic spindle poles and midzone microtubules during metaphase (9). Following activation by the LIM protein ajuba in G_2, aurora A phosphorylates and recruits several microtubule-associated proteins to the centrosome to promote maturation. After the breakdown of the nuclear envelope, inactive cytoplasmic aurora A is transported to the proximal ends of the microtubules and activated by the spindle protein TPX2, where it plays an as yet not fully defined role in the Ran-spindle assembly process (9, 13). Aurora A is also linked to the process of G_2-M transition, with suppression of expression leading to G_2-M arrest and apoptosis and ectopic expression leading to bypass of the G_2-M DNA damage-activated checkpoint in model systems (15, 16). In experimental murine models, overexpression of aurora A was found to be oncogenic (17, 18).

Aurora B is the catalytic component of the chromosomal passenger complex, which is composed of three additional noncatalytic subunits that direct its activity: survivin, INCEP, and borealin. The chromosomal passenger complex orchestrates the accurate segregation of the chromatids at mitosis, histone modification, and cytokinesis (19). Aurora B and its chromosomal passenger complex partners are associated with the centromeres from prometaphase to metaphase. After chromatid separation, they relocate to the midzone and remain at the midbody until the completion of cytokinesis (9). Aurora B function has been linked to chromatin modification in relation to the phosphorylation of histone H3 at Ser^{10} and Ser^{28} (20), events that may be required for chromosome condensation. Through the phosphorylation of MCAK, this kinase also has a crucial role in the regulation of accurate chromatid separation, with aurora B activity ensuring that mitosis does not proceed until all chromosomes have bipolar undertension attachments (21). Aurora B is also thought to be involved in the recruitment of spindle checkpoint proteins to the kinetochores. Finally, this kinase has a critical role in cytokinesis, with depletion resulting in polyploidy cells as a consequence of cytokinesis failure (9). High-level expression of aurora B in model systems has been linked to chromosome instability (22, 23).

Aurora C does not seem to have a role in mitosis in the majority of normal cells, with expression essentially restricted to the testes. Localizing in a similar pattern to aurora B, it is thought that aurora C is also a catalytic chromosomal passenger protein. Indeed, it has been shown that aurora C can rescue aurora B–depleted cells, suggesting some significant overlap in function (24). It is therefore thought likely that aurora C has a specific role in the regulation of chromosome segregation during male meiosis (25).

Aurora Kinases as Anticancer Targets: Preclinical Data

In a wide range of tumor types compared with essentially nonproliferating matched normal tissue, aurora A is strongly expressed at high frequency. This high level of expression is often associated with amplification of the region of chromosome 20 encoding *AURKA* (Table 1), indicating that deregulated expression of at least one gene in the amplified region provides a survival/proliferation advantage to the tumor cell and is therefore linked directly to neoplasia. In contrast, the chromosomal region encompassing *AURKB* does not seem to be amplified to a high level in tumors, although low-level copy number increases have been noted in non–small cell lung cancer (NSCLC; ref. 26). The *AURKB* gene, however, has also been shown to be strongly expressed in many tumor types compared with essentially nonproliferating matched normal tissue, with expression levels often correlating with disease characteristics or outcome (Figs. 2 and 3; Table 1). For example, we determined the expression of both aurora A and aurora B by immunohistochemistry in 33 patients with previously untreated, advanced NSCLC (Fig. 2).[4] Our study revealed strong nuclear staining for aurora A (Fig. 2A) and aurora B (Fig. 2B) in 12 (36%) and 7 (21%) cases, respectively. Furthermore, aurora A positivity correlated with aurora B positivity ($P = 0.01$, Fisher's exact test) and with p53 overexpression ($P = 0.05$). When considering such data, it should be noted that the differential expression of a gene in tumor compared with normal tissue per se may be a poor indicator of causal involvement in neoplasia, given that this expression may simply be appropriate for the current physiologic state of the

[4] Unpublished data.

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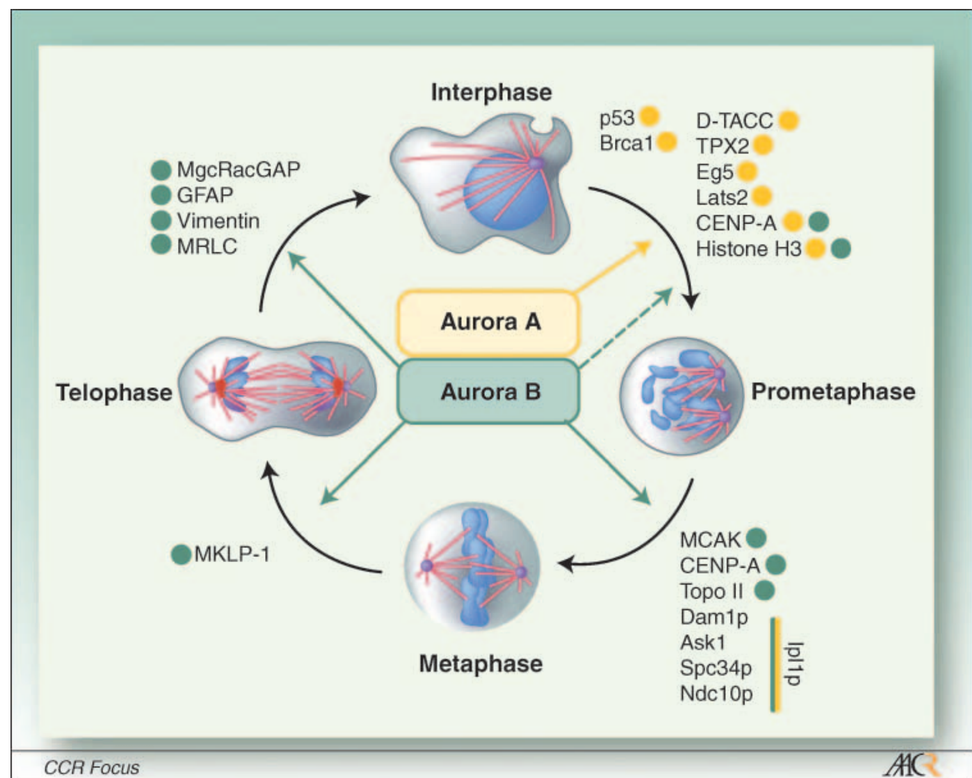

Fig. 1. Cell cycle execution points and targets of aurora A and B kinases. Substrates phosphorylated in each phase of the cell cycle by each kinase are detailed, with orange circles denoting targets of aurora A and green circles denoting targets of aurora B. Orange/green line, known substrates of the single yeast aurora kinase Ipl1p. Adapted with permission from Macmillan Publishers Ltd: Oncogene (13), 2005.

tumor cells. This may be particularly relevant in the context of cell cycle–associated genes such as aurora kinases, which are dramatically up-regulated in highly proliferating compared with nonproliferating cells. Thus, elevated *AURKA* or *AURKB* tumor expression may be an indicator of rapid cell division, an effect rather than a cause of the malignant phenotype. Such a possibility is supported by the concurrent up-regulation of both *AURKA* and *AURKB* transcription observed in tumors (26). In addition, to show that *AURKB* is strongly expressed in the majority of NSCLC cases with high-level expression of the gene correlating with poor survival and tumor genetic instability, however, we have also shown that, in most informative cases, this expression seems to be driven from one chromosomal allele (26). These observations are consistent with the hypothesis that up-regulation of the gene occurs through somatically acquired *cis*-located genetic damage, implicating aberrant deregulated expression of *AURKB* in NSCLC carcinogenesis. Aurora C expression has also been noted in some tumor cell lines, but the significance of this observation is not yet clear (11).

It would seem that activating mutations of aurora kinase genes are rare in human tumors (27). Several studies, however, have suggested that commonly occurring gene polymorphisms of *AURKA* and *AURKB* are associated with cancer risk or clinical outcome among diverse ethnic groups (Table 1). Although these data imply that differences in functionality or basal expression levels of these kinases may modify risk, perhaps through marginally increasing the level of genetic instability in normal cells (12), they do not provide additional supportive evidence for aurora kinases as potentially effective anticancer drug targets. In some ways, such a statement may seem to be counterintuitive. Yet, when considering such data, we must discriminate between the process of carcinogenesis and the therapeutic utility of targeting a particular protein in an established tumor. For example, if a particular base change alters gene function in such a way as to marginally increase the chance of genetic instability in a particular cell type, this genotype may strongly modify the lifetime risk of tumorigenesis for a carrier. Despite being strongly implicated in elevated cancer risk, however, the gene product may still not be an effective anticancer drug target in relation to the clinical treatment of recognizable disease. Simply, once the horse has gone, fixing the lock on the stable door will not bring it back.

The clearly established involvement of aurora kinases in the process of mitosis and the strong circumstantial evidence suggesting that deregulated expression of aurora A and B is linked to tumorigenesis spurred the drive to identify pharmacologically active small-molecule inhibitors of these kinases. The compounds identified reacted with more than one kinase subtype or else were specific for one or other aurora kinase (Table 2). *In vivo* studies with several of these agents were promising, showing that they were able to bring about a profound inhibition of tumor growth in a range of model systems (28–30). Coupled with the genomic data, such studies provided a strong rationale to underpin subsequent clinical investigations. As is generally the case, however, it was not clear from the preclinical data whether aurora kinase inhibitors, if clinically active in humans, would function primarily as cytotoxic (associated with tumor cell death and response) or

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cytostatic (associated with growth inhibition and disease stabilization) agents. Ultimately, this question could only be addressed in clinical studies.

Inhibitors of Aurora Kinases

Of the many aurora-selective small-molecule inhibitors currently undergoing preclinical and clinical assessment, only the clinically most advanced inhibitors are briefly discussed here, whereas many other promising members of this new drug class are in development (Table 2).

MK-0457 (VX-680) is a pyrimidine derivative with affinity for aurora A, B, and C at nanomolar concentrations. MK-0457 prevents cytokinesis but allows cells to progress through the other stages of mitosis, which leads to polyploidy and, in some cancer cell lines, massive apoptosis. In preclinical models, MK-0457 blocked tumor xenograft growth and induced tumor regressions (28). In its first phase I clinical trial, MK-0457 was given as an i.v. continuous infusion over several days to patients with previously treated solid tumors (31). The principal dose-limiting toxicity (DLT) was grade 3 neutropenia, accompanied by some nonspecific side effects, including

Table 1. Aurora kinases in cancer

Alteration	Cancer type	Aurora kinase	Correlation	Study
Overexpression	Breast	AURKA	NA	Tanaka et al. (51)
		AURKA	Chromosomal instability, high grade, ER/PR negativity	Miyoshi et al. (52)
		AURKA	Centrosome anomaly	Hoque et al. (53)
		AURKA	Nuclear grade	Royce et al. (54)
	Lung	AURKA	NA	Smith et al. (26)
		AURKA	Poor differentiation	Xu et al. (55)
		AURKB	Genetic instability	Smith et al. (26)
		AURKB	Lymph node invasion	Vischioni et al. (56)
	Pancreas	AURKA	NA	Li et al. (57)
	Prostate	AURKB	Grade, proliferation	Chieffi et al. (58)
	Bladder	AURKA	Tumor recurrence	Comperat et al. (59)
		AURKA	Tumor T stage	Fraizer et al. (60)
	Esophagus	AURKA	NA	Tong et al. (61)
		AURKA	NA	Yang et al. (62)
	Brain	AURKB	Grade, outcome	Araki et al. (63)
		AURKB	Survival	Zeng et al. (64)
	Liver	AURKA	Grade, stage	Jeng et al. (65)
	Head/neck	AURKA	NA	Zhao et al. (66)
		AURKA	Centrosomal amplification	Li et al. (67)
		AURKA	Progression, survival	Reiter et al. (68)
		AURKB	Proliferation, histologic differentiation, and metastasis	Qi et al. (69)
	Thyroid	AURKB	Grade, proliferation	Sorrentino et al. (70)
	Ovarian	AURKA	Posttreatment survival	Lassmann et al. (71)
		AURKA	Survival	Landen et al. (72)
	Renal	AURKA	No association detected	Kurahashi et al. (73)
Amplification	Breast	AURKA	BRCA2, TP53 mutation	Bodvarsdottir et al. (74)
		AURKA	NA	Sen et al. (75)
	Colon	AURKA	Genetic instability	Nishida et al. (76)
		AURKA	Overexpression	Bischoff et al. (17)
	Brain	AURKA	Overexpression	Reichardt et al. (77)
		AURKA	NA	Klein et al. (78)
		AURKA	Survival	Neben et al. (79)
	Bladder	AURKA	Aneuploidy, grade, outcome	Sen et al. (80)
	Head/neck	AURKA	NA	Tatsuka et al. (81)
	Endometrium	AURKA	NA	Moreno-Bueno et al. (82)
Polymorphisms	Colon	AURKA	Cancer risk (F31I)	Chen et al. (83)
		AURKA	Cancer risk (F31I)	Hienonen et al. (84)
		AURKA	Aneuploidy (F31I)	Ewart-Toland et al. (85)
	Breast	AURKA	Cancer risk (F31I)	Lo et al. (86)
		AURKA	Cancer risk (F31I)	Vidarsdottir et al. (87)
		AURKA	Cancer risk (F31I)	Cox et al. (88)
		AURKB	Cancer risk (S295S)	Tchatchou et al. (89)
	Esophagus	AURKA	Cancer risk (F31I, V57I)	Kimura et al. (90)
	Lung	AURKA	Reduced cancer risk (F31I)	Gu et al. (91)
	Gastric	AURKA	Risk of disease progression (V57I)	Ju et al. (92)
	Multiple	AURKA	Cancer risk (F31I)	Ewart-Toland et al. (93)

Abbreviations: NA, not addressed; F, phenylalanine; I, isoleucine; S, serine; V, valine; ER, estrogen receptor; PR, progesterone receptor.

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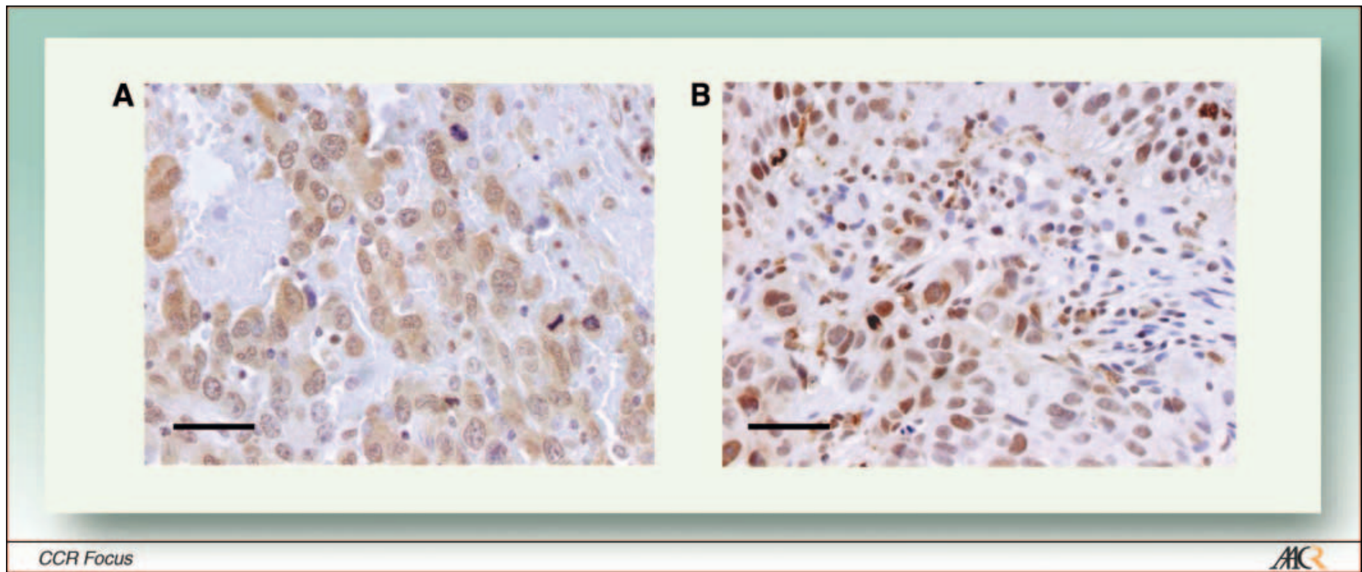

Fig. 2. Coexpression of aurora A and aurora B in lung cancer. Representative aurora immunohistochemistry in NSCLC, showing coexpression of aurora A (*A*) and aurora B (*B*). Bar, 50 μm. (O. Gautschi et al., unpublished data).

low-grade nausea and fatigue. Disease stabilization was observed in one patient with lung cancer and in one patient with pancreatic cancer. Single-agent efficacy studies in lung cancer and colorectal cancer are ongoing.

AZD1152 is a quinazoline prodrug, which is converted in plasma into its active metabolite AZD1152-HQPA, which in turn has high affinity for aurora B and C. The effects of AZD1152-HQPA in cancer cells are comparable with MK-0457 (30). In preclinical models, AZD1152 significantly inhibited the growth of human tumor xenografts. In a phase I clinical trial, AZD1152 was given as a weekly 2-h infusion to patients with advanced, pretreated solid tumors (32). DLT was grade 3 neutropenia, with few nonhematologic toxicities. Pharmacokinetic studies confirmed rapid conversion of AZD1152 into AZD1152-HQPA. Three patients had stable disease (melanoma, nasopharyngeal carcinoma, and adenoid cystic carcinoma). Follow-up studies are ongoing with biweekly and continuous infusions, based on preclinical tumor models, which suggested that prolonged drug administration significantly increased the proapoptotic effect of AZD1152-HQPA.

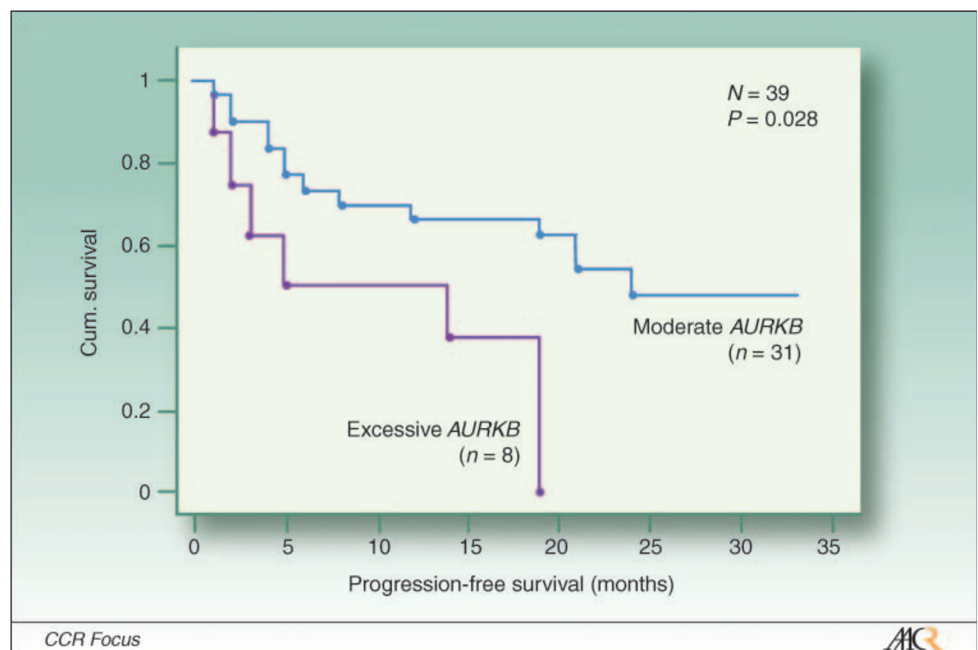

Fig. 3. Prognostic significance of aurora B expression in lung cancer. Aurora B mRNA levels in 39 patients with NSCLC were quantified by real-time reverse transcription-PCR. Patients with excessive (above median) expression had a significantly ($P = 0.028$, Kaplan-Meier curve, log-rank test) poorer survival than patients with moderate (below median) expression. Adapted with permission from Macmillan Publishers Ltd: British Journal of Cancer (26), 2005.

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Table 2. Aurora kinase inhibitors in clinical development

Inhibitor	Target	Administration	Phase I DLT	Best response	Current status
MK-0457 (VX-680; Merck; ref. 31)	Aurora A (K_i = 0.66 nmol/L)	I.v. (continuous i.v. 5 d every 4 wk)	Neutropenia	Remission (leukemia)	Phase II
	Aurora B (K_i = 18 nmol/L)			Stable disease (solid tumors)	
	Aurora C (K_i = 4.6 nmol/L) FLT3 (K_i = 30 nmol/L) BCR-ABL T315I JAK				
AZD1152 (AstraZeneca; ref. 32)	Aurora B (K_i = 0.3 nmol/L)	I.v. (2 h weekly or continuous i.v. 7 d)	Neutropenia	Stable disease (solid tumors)	Phase II
	Aurora C (K_i = 17 nmol/L)				
PHA-739358 (Nerviano; ref. 33)	Aurora A (IC_{50} = 27 nmol/L)	I.v. (1 d every 2 wk)	Neutropenia	Stable disease (solid tumors)	Phase II
	Aurora B (IC_{50} = 35 nmol/L) Aurora C (IC_{50} = 120 nmol/L) FLT3 (IC_{50} = 390 nmol/L) BCR-ABL T315I				
MLN8054 (Millennium; ref. 35)	Aurora A (IC_{50} = 5 nmol/L)	Oral	Somnolence	Stable disease (solid tumors)	Phase I
R763 (Merck/Serono)	Aurora B	Oral and i.v.	NA	NA	Phase I
AT9283 (Astex)	Aurora A (IC_{50} < 3 nmol/L) Aurora B (IC_{50} < 3 nmol/L) BCR-ABL T315I JAK2	Oral and i.v.	NA	NA	Phase I
CYC116 (Cyclacel)	Aurora A/B VEGFR2	Oral	NA	NA	Phase I

Abbreviations: NA, data not available; K_i, dissociation constant for inhibitor binding; JAK, Janus-activated kinase; VEGFR2, vascular endothelial growth factor receptor 2.

PHA-739358 is a pan-aurora (A, B, and C) inhibitor with documented antitumor activity in multiple tumor xenograft models, which have shown sustained tumor growth inhibition after discontinuation of treatment. The results of two phase I dose-escalation studies are available (33). The first study tested 6-h i.v. infusions on days 1, 8, and 15 on a 4-week cycle in patients with advanced, pretreated solid tumors. In a preliminary assessment, DLT was reported to be grade 3 to 4 neutropenia. No tumor responses were observed, but 8 of 40 patients had stable disease for at least 4 months. Pretreatment and posttreatment skin biopsies showed down-regulation of phosphorylated histone H3 Ser^{10} levels in eight of nine patients tested. The second study tested 24-h infusions in a 2-week cycle. Again, DLT was reported to be grade 3 to 4 neutropenia. Nonhematologic toxicities, including fatigue, pyrexia, and diarrhea, were mild. Although no objective tumor responses were observed, 11 of 40 patients achieved disease stabilization. Posttreatment skin biopsies showed decreased phosphorylated histone H3 Ser^{10} levels in four of five patients tested. The recommended phase II dose was 500 mg/m^2 without granulocyte colony-stimulating factor, whereas further dose escalation with filgastrim support is currently being investigated.

MLN8054 was the first orally available aurora kinase inhibitor and the first aurora A–selective inhibitor to enter human clinical trials. This compound induced mitotic accumulation and spindle defects and inhibited proliferation in multiple human cancer cell lines (34). Growth of human tumor xenografts in nude mice was inhibited after oral administration at well-tolerated doses, and the tumor growth inhibition was sustained after discontinuation of treatment. In xenografts, MLN8054 induced mitotic accumulation and apoptosis. The preliminary results of a phase I dose-escalation study are interesting for several reasons (35). Oral MLN8054 (daily on 7 consecutive days, 21-day intervals) was rapidly absorbed and displayed dose-proportionate exposure. DLT was found to be reversible grade 3 somnolence and no profound myelosuppression occurred. This was consistent with animal studies, which showed that MLN8054 binds to the γ-aminobutyric acid α 1 benzodiazepine receptor and causes reversible somnolence. Three human patients with metastatic colorectal cancer received eight cycles of treatment consistent with stable disease. Importantly, immunohistochemical analysis of skin biopsies did not show significant accumulation of cells in mitosis, suggesting incomplete target inhibition. Based on these results, the study is now escalating twice-daily dosing of MLN8054 over 14 days, with the coadministration of methylphenidate.

New Directions

Whether aurora A or aurora B is the better anticancer drug target is a matter of debate (8). At least two groups have directly addressed this question in the laboratory. Warner et al. (36) compared the effects of aurora A and aurora B antisense oligonucleotides in pancreatic cancer cells and found that aurora

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A – targeted therapy may be preferable to aurora B targeting, as shown by mitotic arrest and the rapid induction of apoptosis. Girdler et al. (37) compared the effects of RNA interference and small molecules targeting aurora A versus aurora B in colon cancer cells and found that the cells tested were extremely sensitive to aurora B inhibition. Interestingly, dual inhibition of aurora A and B results in phenotypes identical to inactivation of aurora B alone (28). Using RNA interference experiments, Yang et al. (38) showed that inactivation of aurora B indeed bypasses the requirement for aurora A and leads to polyploidy, indicating that aurora B is responsible for mitotic arrest in the absence of aurora A.

With the emergence of a large number of aurora kinase inhibitors, it will be interesting to see which, if any, of the currently available agents will have the requisite degree of antitumor activity in patients or merit further clinical development. Harrington et al. (28) showed that MK-0457 targets the FLT3 kinase and thereby ablated colony formation in primary acute myelogenous leukemia cells with FLT3 internal tandem duplications. Giles et al. (39) recently reported on the induction of clinical remission with MK-0457 in three patients with BCR-ABL – positive, pretreated leukemia and showed that MK-0457 blocked the T315I-mutant BCR-ABL kinase in these patients. These cases document the first objective responses to a kinase inhibitor in the T315I-mutant BCR-ABL and spurred ongoing clinical trials with MK-0457 in leukemia. The results also indicate that, analogous to sorafenib (which was initially designated as a RAF inhibitor and then later was found to additionally block angiogenesis), off-target effects may add to the successful clinical development of aurora kinase inhibitors. Further, we propose that the lack of objective tumor regression in early clinical trials of aurora kinase inhibitors in solid tumors warrants alternative assessments of antitumor activity in the phase II setting, such as the use of disease control rate (response rate plus stable disease), time-related end points, or randomized discontinuation study designs. This is especially relevant in the context of recent observations that some targeted agents (e.g., sorafenib and erlotinib) induced modest tumor regressions in phase II trials but have subsequently shown to improve survival outcomes in randomized phase III trials (40, 41).

Are the aurora kinase inhibitors cancer specific? Clearly, given that they are key regulators of mitosis, they are not, in the strictest sense. Indeed, neutropenia was the primary dose-limiting phase I toxicity in several studies, suggesting that these agents have collateral antiproliferation toxicity on the bone marrow. Aurora kinase inhibitors have also been shown to induce polyploidy in normal mammary epithelial cell cultures (42), raising the issue of long-term clinical effects. Clinical tolerability has generally been good, however, and no severe mucositis, peripheral neuropathy, diarrhea, or alopecia has been observed. One question for the future will therefore be: are there tumors that are exceptionally sensitive to such compounds, enabling delivery of minimally toxic doses that have significant antitumor effects? The identification of biomarkers predictive of clinical benefit for a particular drug in a particular patient may therefore be critical in relation to the effective development of new anticancer agents. In the future, it is likely that many new classes of biological marker, including mutational, epimutational, gene expression, and functional assays, will affect clinical decisions relating to which drug to use, at which dose, and in which patient. The collection of material to facilitate such studies will become increasingly important, especially in the larger clinical trials. The importance of biomarkers in evaluating the question of whether a drug hits a cellular target has also become increasingly accepted in oncology. This is especially true for newer drugs that may be associated with minimal toxicity and where the maximum tolerated dose may not be reached in phase I studies. One particularly attractive feature of the development of aurora kinase inhibitors is the availability of functional biomarkers of target effect. Analysis of phosphorylated histone H3 Ser^{10} levels can show the effects of both aurora A and aurora B inhibitors (Fig. 4). Because aurora A inhibition results in accumulation in mitosis, levels of phosphorylated histone H3 Ser^{10} may increase. In contrast, aurora B inhibition is expected to decrease the levels of phosphorylated histone H3 Ser^{10} because this is a direct substrate of aurora B kinase. As indicated by the translational study for PHA-739358 mentioned previously, confirmation of this as a sensitive and specific biomarker in clinical samples could offer the potential to bring a predictive biomarker to the clinic (33). Additional biomarkers have also been proposed. For example, Gizatullin et al. (43) studied the effect of cell cycle control on the effect of MK-0457 in cell lines from lung, breast, and colon cancer and found that a defective p53-p21 pathway was associated with increased sensitivity. Galvin et al. (44) reported on the use of the aurora A-T288 autophosphorylation site as pharmacodynamic markers for MLN8054. Mitotic index measurements coupled with the aurora A-T288 autophosphorylation site was a direct marker of aurora A activity in tumor and skin biopsies. These studies represent significant advances in the development of clinical biomarkers for aurora kinase inhibitors. Thus, predictive markers, and markers that allow determination of whether a drug is able to reach the target in a given patient, offer a great chance to achieve the truly individualized therapy that academic oncologists have imagined for the future.

Several promising drug combinations, including aurora kinase inhibitors, are emerging. Setting the stage, Hata et al. (45) showed the synergistic enhancement of taxane activity in the presence of aurora A RNA interference in pancreatic cancer cells. Yang et al. (46) found that knockdown of aurora A by RNA interference reduced phosphorylated AKT levels and sensitized ovarian cancer cells to cisplatin. Sun et al. (47) described similar results in ovarian and lung cancer cells exposed to MK-0457 plus etoposide. Lee et al. (48) again described additive toxicity with MK-0457 and doxorubicin in prostate cancer cells, whereas Tanaka et al. (49) reported significantly enhanced docetaxel activity by aurora A short hairpin RNA in esophageal cancer xenografts *in vivo*. Tao et al. (50) showed preliminary data indicating that AZD1152 increased radiosensitivity *in vivo* and that this effect was p53 and cell cycle dependent. How aurora kinase targeting interacts with chemotherapy and radiation at the molecular and cell cycle level remains to be determined, but these results are very encouraging and will affect the design of clinical studies with aurora kinase inhibitors in the near future.

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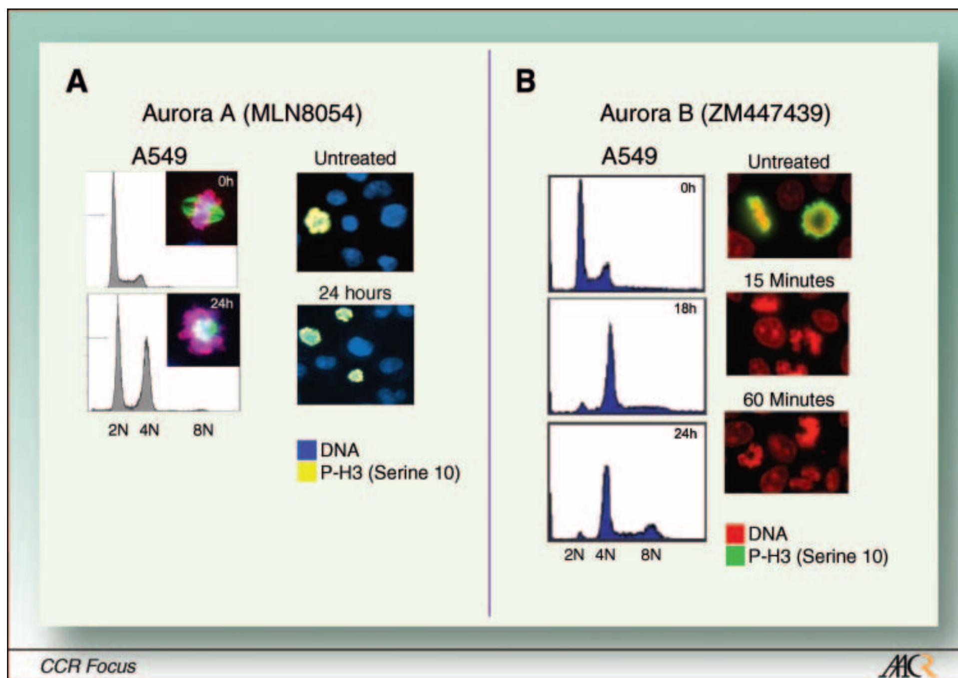

Fig. 4. Induction of characteristic phenotypes by different aurora kinase inhibitors. *A,* in the A549 NSCLC cell line, aurora A – specific inhibitor MLN8054 induces monopolar spindles (inlay, *green color*), circular chromatin (inlay, *purple color*), and accumulation in mitosis (increased 4N peak in flow cytometry, increased phosphorylated histone H3 Ser^{10} staining). (O. Gautschi et al., unpublished data.) *B,* in contrast, aurora B/C – specific inhibitor ZM447439 in the A549 cell line allows for progression through mitosis, decreases phosphorylated histone H3 Ser^{10} staining, blocks cytokinesis, and induces polyploidy (appearance of 8N peak in flow cytometry). Reproduced from the Journal of Cell Biology, 2003;161:267-80. Copyright 2003 The Rockefeller University Press.

Conclusion

Genetic instability is a key driver of carcinogenesis, and there is ample evidence to suggest that deregulation of aurora kinases contributes to the acquisition of genetic aberrations, promoting the development of malignancy. The importance of aurora kinases as anticancer targets remains to be defined by ongoing clinical trials. Current trials are also aiming to define optimal drug schedules and to maximize target inhibition. At present, no predictive biomarker is available to select patients for treatment with an aurora kinase inhibitor, and further progress in this area is needed. Accumulating preclinical data point toward additive or even synergistic anticancer effects between aurora kinase inhibitors and conventional chemotherapy, and much hope lies on the translation of such combinations into the clinic.

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