Chromosoma (2013) 122:431–449
DOI 10.1007/s00412-013-0419-8

REVIEW

Mitosis as an anti-cancer drug target

Anna-Leena Salmela · Marko J. Kallio

Received: 23 January 2013 / Revised: 23 May 2013 / Accepted: 27 May 2013 / Published online: 18 June 2013

Abstract Suppression of cell proliferation by targeting mitosis is one potential cancer intervention. A number of existing chemotherapy drugs disrupt mitosis by targeting microtubule dynamics. While efficacious, these drugs have limitations, i.e. neuropathy, unpredictability and development of resistance. In order to overcome these issues, a great deal of effort has been spent exploring novel mitotic targets including Polo-like kinase 1, Aurora kinases, Mps1, Cenp-E and KSP/Eg5. Here we summarize the latest developments in the discovery and clinical evaluation of new mitotic drug targets.

Keywords Anti-mitotics · LMW inhibitors · Mitosis · Cancer · Drug development

Introduction

Cell division (termed mitosis in somatic and meiosis in germ cells) is a fundamental process in the life cycle of a cell. Equal distribution of chromosomes between the daughter cells is essential for the viability and well-being of an organism: loss of fidelity of chromosome segregation is a contributing factor in human cancer and also gives rise to miscarriages and genetic birth defects. For maintaining the proper chromosome number, a cell must prevent cell division until its accuracy can be guaranteed. For this purpose, an evolutionarily conserved signalling cascade, the spindle assembly checkpoint (SAC), has evolved (Musacchio and Salmon 2007; Suijkerbuijk and Kops 2008; Zich and Hardwick 2010). The checkpoint is comprised of a complex network of proteins that relay and amplify anaphase-inhibiting signals created by the kinetochores (KTs) that are unattached or incorrectly attached to the spindle microtubules (MTs). The SAC works to prevent anaphase and mitotic exit in the presence of spindle defects and chromosome alignment errors, and therefore it is crucial for genomic stability.

Abnormal chromosome number (aneuploidy) is a hallmark of human cancers (Jallepalli and Lengauer 2001). Aneuploidy is a consequence of segregation errors in mitosis or meiosis which may result from diverse cell division defects, such as multipolarity, abnormal centrosome number, cohesion defects, erroneous cytokinesis and faulty SAC signalling (Chi and Jeang 2007; Decordier et al. 2008; King 2008). Most cancer cells exhibit chromosomal instability (CIN); in other words, they continuously loose or gain whole chromosomes or their fractions at elevated rates. Rather than being merely a characteristic of tumor cells, aneuploidy is a contributing factor in tumorigenesis. Almost 100 years ago, Theodor Boveri presented his hypothesis on the origin of cancer (Boveri 1914), stating that an incorrect combination of chromosomes inherited by a single cell may be an underlying cause for malignant cell transformation (Hardy and Zacharias 2005). To date, Boveri's theory is supported by numerous in vitro and in vivo studies. Aneuploidy and CIN are indeed hallmarks of cancer cells, and their high levels often correlate with poor patient prognosis (Bakhoum et al. 2011; Choi et al. 2009; Heilig et al. 2010) and tumor grade (Kronenwett et al. 2004). CIN can be observed in the premalignant stage in colorectal tumorigenesis, which strengthens the notion that allelic imbalance can drive tumor formation (Shih et al. 2001). Moreover, germline mutations in SAC protein BubR1 have been identified as a cause of a rare cancer-susceptible disorder, mosaic variegated aneuploidy (Hanks et al. 2004, Suijkerbuijk et al. 2010). Mouse models with deregulated expression of specific SAC proteins manifest an increased aneuploidy and CIN, and the cancer susceptibility of these mice is frequently elevated in non-perturbed conditions or upon treatment with carcinogenic compounds (Dai et al. 2004; Iwanaga et al. 2007; Jeganathan et al. 2007; Weaver and Cleveland 2007). It is important to note that CIN has not only a role in tumorigenesis but it can also confer resistance to chemotherapeutic drugs (Lee et al. 2011; Swanton et al. 2009). On the other hand, birth defects, in which the

A.-L. Salmela · M. J. Kallio (✉)
VTT Biotechnology for Health and Wellbeing, VTT Technical Research Centre of Finland, Itäinen Pitkäkatu 4C, Pharmacity Bldg, 4th Floor, P.O. Box 106, 20521, Turku, Finland
e-mail: marko.kallio@vtt.fi

underlying cause is aneuploidy, increase the susceptibility to certain cancers, for example children with Down syndrome have high risk of leukaemia (Hasle et al. 2000). Yet, investigating how aneuploidy and CIN contributes to tumorigenesis is complex and unresolved questions still remain as for example the debate over whether aneuploidy has a causal role in cellular transformation and how the other features such as genetic context of the tissue influences the outcome of aneuploidy (Kops et al. 2005; Holland and Cleveland 2012; Weaver et al. 2007; Weaver and Cleveland 2008).

While chromosome missegregation may be tumorigenic due to the gain or loss of a critical gene function, it may also bring about changes that are detrimental to the viability of a tumor cell (Weaver and Cleveland 2007; Thompson and Compton 2008). The outcome of aneuploidy seems to depend at least on the cell type and the genetic background (Weaver et al. 2007; Sotillo et al. 2010). For example, loss of tumor suppressor p53 and/or retinoblastoma (Rb) promotes tumorigenesis both in vitro and in vivo upon upregulation of Mad2 (Sotillo et al. 2010). However, the adaptation capacity of cancer cells to aneuploidy is not unlimited, for example, reducing levels of SAC proteins BubR1 and Mad2 trigger cancer cell killing as a consequence of massive chromosome loss (Janssen et al. 2009; Kops et al. 2004). Moreover, the cancer cell killing efficacy of MT-targeting drugs such as dosetaxel, which at low nanomolar concentrations induces a transient mitotic delay followed by catastrophic exit from mitosis, may at least partially depend on the induction of aneuploidy (Ikui et al. 2005; Paoletti et al. 1997). However, the clinical relevance of the MT drug concentrations used in vitro and their cell killing effects in vivo remain poorly understood. The therapeutic potency of non-MT anti-mitotic drug development strategies pursued typically rely on induction of cell death from mitotic arrest or generation of a high level of chromosome instability that exceeds the adaptation capacity of cancer cells. How much the future anti-mitotics will advance the treatment of cancer and what their competitive edge will be in comparison to the other cancer therapeutics remain to be seen. Moreover, for most, if not all, the anti-mitotic compounds in development there is no direct data linking the anti-tumor effects with the target inhibition in vivo.

This review provides an overview of possibilities to utilize mitosis as an anti-cancer drug target. At the moment, classical MT drugs are the most important anti-mitotic agents used in the clinics. However, there is a great need for the discovery of novel strategies to target heterogenic tumor cell populations with fewer side effects. Several mitotic non-MT proteins have raised interest as potential therapeutic targets, and a variety of experimental low molecular weight (LMW) compounds have been developed and some of them have advanced to clinical trials. Despite some encouraging exceptions, many anti-mitotics have failed in the clinical trials, for example, due to their cytotoxic effects or inadequate efficacy. We give an update on these inhibitors and summarize the current understanding on their mechanism of action. Finally, the challenges of mitosis-specific therapeutics are shortly discussed.

SAC as a target of LMW compounds

While moderate SAC defects may predispose to tumorigenesis, complete inactivation of the checkpoint is lethal (Kops et al. 2005, 2004). The essential nature of the SAC has created the concept of "mitotic drivers" (Keen and Taylor 2009) referring also to potential anti-cancer drug candidates that suppress the activity of SAC and force cells out of abnormal mitosis, thereby inducing massive genetic imbalance. To date, the majority of the experimental compounds that cause premature mitotic exit inhibit the activity of Aurora B kinase. However, other SAC kinases, such as Bub1 (Gao et al. 2009) and Mps1 (Colombo et al. 2010; Kwiatkowski et al. 2012; Lan and Cleveland 2010; Tardif et al. 2011), have also raised interest as potential drug targets. The outcome of a forced mitotic exit is typically vast aneuploidy or, if cytokinesis is prevented, tetraploidy. Subsequently, the cells may undergo cell death, senescence or endocycling (Keen and Taylor 2009).

Pre-clinical data suggest that tumor cells might be more vulnerable to inhibition of SAC proteins such as Aurora B and Mps1 (Kwiatkowski et al. 2010; Stolz et al. 2009). For instance, it has been shown that Mps1-In-1, a LMW inhibitor of Mps1, decreases the proliferative capacity of cells and abolishes the viability of both tumor and non-cancerous cell types but induces apoptosis-associated PARP cleavage only in the malignant cells. Moreover, there is evidence that Aurora B inhibitor Gö6976 lowers cells proliferation capacity and induces PARP cleavage in cancer cells, whereas non-transformed cells are not markedly affected. The basis for the possible cancer cell selectivity of SAC inhibition is not well understood. Inhibition of mitotic proteins in cancer therapy relies on the assumption that tumor cells proliferate rapidly, and therefore the fraction of cells expressing the target proteins is high in the malignant tissue. Moreover, mitotic proteins are often overexpressed in tumor cells, making the target even more abundant. It is also possible that due to the presence of extra chromosomes, the cancer cells spend an abnormally long time in early mitosis which can sensitize the cells to the SAC override (Janssen and Medema 2011). Furthermore, aneuploid cancer cells might be more sensitive than normal cells to further genetic imbalances that anti-mitotic drugs induce (Janssen and Medema 2011).

MT inhibitors

MT poisons compose a family of therapeutics which has a long history as cancer drugs with great overall clinical

success. When these drugs are used at high concentrations, MTs are either stabilized (taxanes and epothilones) or depolymerized (vinca alkaloids). In vitro low drug concentrations do not affect the mass of the MT polymers but suppress MT dynamics in cells (Panda et al. 1996; Yvon et al. 1999). However, whether the same is true in vivo remains to be confirmed. Taxanes are widely used to treat Kaposi's sarcoma, non-small-cell lung cancer and cancers of breast, ovarian, prostate, whereas vinca alkaloids are primarily utilized in the treatment of haematological cancers (Jordan and Wilson 2004). The effects of taxanes and vinca alkaloids in cultured cells are well established, but whether the same mechanisms account for clinical efficacy is poorly understood. In cell lines, these drugs induce a SAC-mediated M phase arrest due to the disruption of spindle apparatus function. The drug-treated cells can die in mitosis or undergo mitotic slippage which is followed by cell death, terminal arrest (senescence) or cycling and endoreduplication (Fig. 1) (Keen and Taylor 2009). Mitotic slippage is considered as one of the mechanisms for development of resistance to MT poisons (Chan et al. 2012). Furthermore, this process can in principle predispose to new malignant cell growth if the polyploid cells survive, and upon diminishment of MT drug effect, the multipolar cells divide, creating aneuploidy.

Although commonly used in cancer clinics, traditional MT drugs have major drawbacks (Jordan and Wilson 2004; Schmidt and Bastians 2007). Besides being constituents of the mitotic spindle, MTs have important functions unrelated to cell division. Therefore, side effects such as neuropathy, an impairment of peripheral nervous system function, are commonly encountered. Moreover, enhanced activity of efflux pumps among other mechanisms may lead to drug resistance, which limits the clinical benefits of MT poisons. The lack of cancer cell specificity and the adverse effects of this family of therapeutics are among the main reasons for the search of new precision anti-mitotics.

Novel precision anti-mitotics

The efforts for identifying novel drug candidates within the mitotic machinery have generated LMW compounds against various mitotic proteins, including but not limited to kinases such as Polo-like kinase 1 (Plk1), Aurora A and B, and Mps1, as well as kinesins, such as Cenp-E and KSP/Eg5. In cells, these experimental anti-mitotics cause a SAC-mediated mitotic arrest or, alternatively, a premature forced mitotic exit due to the override of the SAC signalling. The end result is typically perturbation of cell cycle progression and/or suppression of cell proliferation via enhanced apoptosis at mitosis or after a mitotic slippage (Janssen and Medema 2011). It is anticipated that targeting non-MT proteins in M phase would inhibit proliferation in a more cancer cell-specific manner and possibly avoiding the neuropathies associated with the MT poisons in clinical use.

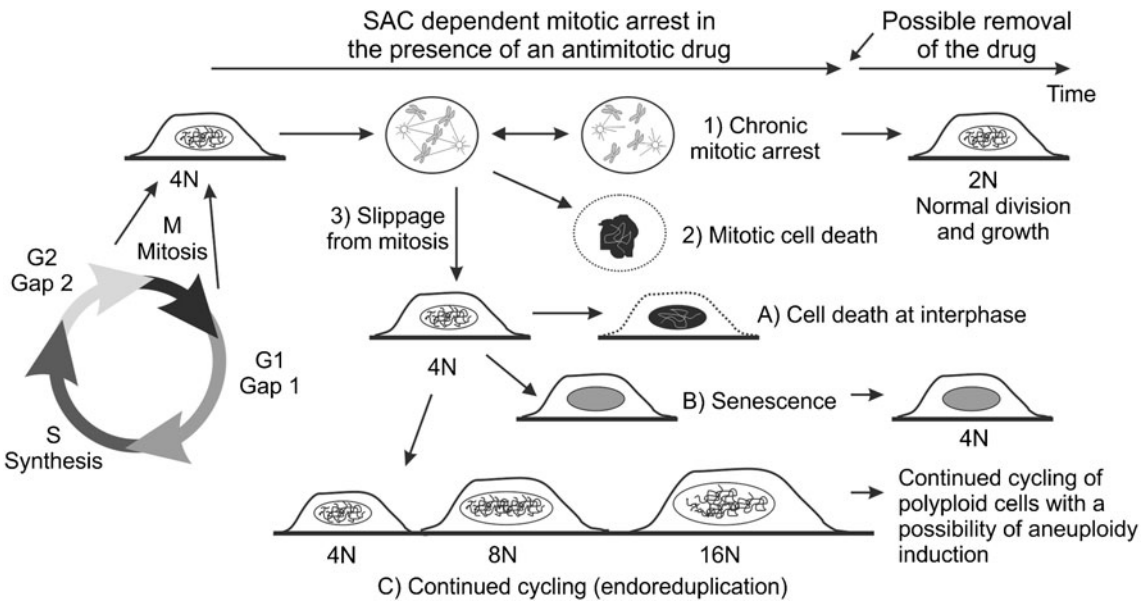

Fig. 1 The possible cellular outcomes of anti-mitotic drug treatment. The cells become affected by the drug as they approach/enter the M phase. Pending the mechanism of action of the drug, the cells can either undergo (*1*) a chronic mitotic arrest that can be a reversible event upon drug withdrawal, (*2*) cell death directly from M phase, or (*3*) adaptation/mitotic slippage/forced mitotic exit. The last option can lead to (*A*) cell death after exit from M phase, (*B*) cellular senescence and survival, or (*C*) continued cycling and endoreduplication which, upon removal of the drug, may generate chromosomal instability via aberrant mitoses (modified from Yamada and Gorbsky (2006))

Kinesin inhibitors

Kinesins are motor proteins that use ATP energy to translocate, often with cargo, along MTs (Rath and Kozielski 2012). To date, 16 kinesins have been shown to have mitotic functions (Rath and Kozielski 2012) in spindle assembly, chromosome alignment and segregation, and cytokinesis. Therefore many of them are considered as attractive drug target candidates. To date, clinical trials have been initiated with inhibitors of kinesin-5 (KSP/Eg5) and Cenp-E, and a handful of experimental compounds are in pre-clinical development (Rath and Kozielski 2012; Huszar et al. 2009). These inhibitors may target the motor activity of the kinesins or force them to tightly bind MTs in a "rigour" state, the latter of which may result in more effective perturbation compared to inhibition of ATP hydrolysis. KSP/Eg5 regulates centrosome separation and, consequently, its inhibition results in a monopolarity and mitotic arrest (Blangy et al. 1995). KSP/Eg5 is overexpressed in various human tumors, but whether this reflects higher proliferation rate of a cell population or true protein excess in the cell population is unclear. Numerous KSP/Eg5 inhibitors have progressed to clinical trials (Rath and Kozielski 2012; Huszar et al. 2009). One of the most advanced is SB-715992, ispinesib, co-developed by Cytokinetics and GlaxoSmithKline. There is clinical evidence on efficacy against breast cancer (Purcell et al. 2010), and phase I results on patients with childhood solid tumors encourage for initiation of phase II studies (Souid et al. 2010). An ispinesib analogue, SB-743921 from Cytokinetics, was evaluated in phase I clinical trial to determine pharmacokinetics and phase II dosing (Holen et al. 2011). At best, clinically effective KSP/Eg5 inhibitors have resulted in stable disease as single agents (Holen et al. 2011; Lee et al. 2008). However, combining KSP/Eg5 inhibitors with other anti-cancer drugs may result in synergistic antiproliferation effects, and these possibilities deserve further investigations (Purcell et al. 2010; Blagden et al. 2008; Jones et al. 2006). KSP/Eg5 inhibitors in clinical trials are mostly non-ATP-competitive compounds that target a unique, induced-fit pocket on KSP/Eg5 (Rickert et al. 2008). Mutations of this target site may lead to drug resistance (Maliga and Mitchison 2006; Tcherniuk et al. 2010), but ATP-competitive inhibitors could be tools to combat against such tumors (Luo et al. 2007; Parrish et al. 2007).

Cenp-E is a plus-end-directed kinesin expressed in G2 and M phases (Yen et al. 1992). Cenp-E overexpression is detected in various tumor tissues (Wood et al. 2008), and its allelic heterozygocity decreases cancer susceptibility in certain mouse models (Weaver and Cleveland 2007), suggesting that inhibition of the Cenp-E activity may possess therapeutic value. In cells, disruption of Cenp-E function causes defects in chromosome behaviour and SAC signalling that lead to erroneous chromosome segregation after a mitotic delay and subsequently result in aneuploidy and cell death (Guo et al. 2012; Kapoor et al. 2006; Putkey et al. 2002; Tanudji et al. 2004; Weaver et al. 2003; Yao et al. 2000). All of these underline the importance of Cenp-E in the stabilization of MT–KT attachments and possibly in the amplification of SAC signals. The crystal structure of the Cenp-E motor domain has been solved (Garcia-Saez et al. 2004), which enables in silico screening for inhibitors of its ATPase activity. To date, three inhibitors, namely, syntelin (Ding et al. 2010), UA62784, (Henderson et al. 2009) and GSK923295 (Wood et al. 2010), have been reported, of which GSK923295 is in clinical trials. UA62784 is poorly soluble, indicating a need for chemical optimization (Henderson et al. 2009). GSK923295 is an allosteric inhibitor of Cenp-E ATPase activity and prevents detachment of the protein from MTs and stabilizes ADP-Pi-Cenp-E-MT complex (Wood et al. 2010). GSK923295 results in mitotic arrest and cell death in pre-clinical models (Wood et al. 2010). A clinical study has been conducted in patients with refractory cancers: a stable disease in one third of the patients and a partial response in one patient were achieved (Chung et al. 2012). Toxicity for this class of agents has been primarily myelosuppression with neutropenia as a dose-limiting factor.

Farnesyl transferase inhibitors

Another means to inhibit Cenp-E activity is to target farnesylation of the kinesin. Although farnesyl transferase inhibitors (FTIs) were originally developed to inhibit the oncogene ras (Kohl et al. 1993), the inhibitors were soon recognized to elicit their effects in a more complex manner. Clinical studies demonstrate anti-tumor activity preferentially against ras-independent cancers (Beaupre et al. 2004; Song et al. 2000). Because FTIs induce a cell cycle arrest at prometaphase, it was suggested that FTIs might target mitotic proteins (Crespo et al. 2001). Mitotic proteins Cenp-E and Cenp-F are known to undergo farnesylation (Ashar et al. 2000a) and thus are plausible candidates for being effectors of FTIs. Prevention of farnesylation in cells induces a phenotype resembling depletion of Cenp-E or Cenp-F: cells exhibit chromosome misalignment, lost sister KT tension and a mitotic delay (Crespo et al. 2002; Schafer-Hales et al. 2007). FTIs have been shown to abolish localization of Cenp-F to the nuclear envelope at G2/M and KTs at prometaphase (Hussein and Taylor 2002) and to prevent both Cenp-E and Cenp-F from localizing to metaphase KTs (Schafer-Hales et al. 2007). Furthermore, FTIs prevent binding of Cenp-E to MTs in vitro (Crespo et al. 2001; Ashar et al. 2000b). On the other hand, a mitotic arrest with a monopolar spindle has been described after FTI treatment, suggesting that the inhibitors may also target protein(s) required for spindle pole separation and spindle assembly (Crespo et al. 2001). Many proteins have been shown to

undergo farnesylation, but it is still unclear which targets mediate the effects of FTIs during mitosis (Harousseau 2007). Clinical trials indicate that FTIs may have therapeutic value in the treatment of hematologic malignancies (Harousseau 2007; Braun and Fenaux 2008) and metastatic breast cancer (Li and Sparano 2008).

Plk1 inhibitors

Plk1 is a key mitotic kinase that is often found overexpressed in a variety of human cancers (McInnes et al. 2005; Takai et al. 2005). The high expression of Plk1 is also associated with poor patient prognosis (McInnes et al. 2005; Takai et al. 2005). Abrogation of Plk1 function causes mitotic arrest followed by apoptosis in several cancer cell lines (Spankuch-Schmitt et al. 2002; Strebhardt and Ullrich 2006). Constitutive overexpression of Plk1 in NIH 3T3 cells stimulates cell transformation, and the cells form tumors in nude mice (Smith et al. 1997), indicating that excess kinase can contribute to cell fate and tumorigenesis. Furthermore, loss of Plk1 confers increased sensitivity to certain chemotherapeutic drugs, such as taxol and herceptin (Spankuch et al. 2006, 2007). The cellular tasks of Plk1 and the clinical potency of its functional perturbation have inspired the development of several inhibitors of kinase. Here, we provide an overview of the Plk1 inhibitors investigated in clinical trials.

Most Plk1 inhibitors are ATP competitors which target the catalytic activity of the kinase via binding to its ATP pocket. To date, five Plk1 inhibitors, three of which are ATP competitors, have entered clinical trials, and several compounds are in pre-clinical development. BI2536, developed by Boehringer Ingelheim, is among the best-characterized anti-Plk1 compounds: it has anti-cancer activity in xenograft models and shows efficacy in phase I trials in patients with solid tumors of different tissue origin (Ellis et al. 2012; Mross et al. 2008; Steegmaier et al. 2007) and with refractory/relapsed non-Hodgkin lymphoma (Vose et al. 2012). Modest anti-tumorigenic effects have been observed in phase II trials in patients with non-small cell lung cancer and hormone refractory prostate cancer (Pandha et al. 2008; Sebastian et al. 2010). BI6727 belongs to the same class of Plk1 inhibitors as BI2536 but possesses improved pharmacokinetics (Rudolph et al. 2009). BI6727 is currently tested in phase II studies with patients with advanced solid tumors (Schoffski et al. 2012). GSK461364A developed by GlaxoSmithKline is a selective ATP-competitive Plk1 inhibitor chemically modified from a thiophene benzimidazole named compound 1 (Gilmartin et al. 2009; Lansing et al. 2007). GSK461364A is anti-proliferative in several tested cancer cell lines and results in tumor regression in xenograft mouse models (Gilmartin et al. 2009). The compound has been subjected to phase I trials for non-Hodgkin's lymphoma (Lapenna and Giordano 2009), and dosing recommendation for phase II trials in patients with advanced solid tumors was recently suggested (Olmos et al. 2011). Finally, an orally administered ATP-competitive Plk1 inhibitor NMS-P937 (Beria et al. 2011) is currently in phase I trials (http://www.nervianoms.com/en/oncology-en/pipeline/nms-1286937.html).

The Polo-like kinase family members possess a specific phosphopeptide-binding domain (polo-box domain, PBD) that is implicated in the subcellular localization and substrate affinity of the Polo-kinases (Elia et al. 2003a; Lee et al. 1998). The PBD recognizes and binds to phosphopeptides which contain a Ser-pThr/pSer-(Pro/X) motif (Elia et al. 2003b). Inhibitors of PBD are thought to be more specific than those targeting the Polo-kinase kinase domain (Strebhardt and Ullrich 2006). To date, three phosphopeptide ligands of PBD have been identified (Strebhardt and Ullrich 2006). Thymoquinone and purpurogallin are natural products inhibiting PBD in in vitro and in vivo cells (Reindl et al. 2008; Watanabe et al. 2009). Poloxin is a synthetic thymoquinone derivative with improved specificity (Reindl et al. 2008). Similarly as the PBD overexpression (Hanisch et al. 2006; Seong et al. 2002), the PBD inhibitors mislocalize Plk1 and induce chromosome alignment defects, causing a SAC-mediated mitotic delay and apoptosis. Although the concentrations needed to elicit the cellular effects are rather high, these compounds validate the PBD as a potential drug target and may serve as hit compounds for chemical optimization.

A number of issues related to the cellular impacts of anti-Plk1 compounds remain to be elucidated before they can be forwarded to clinical trials. For example, the mechanism of cell death by Plk1 inhibitors is not completely understood (Schmidt and Bastians 2007). Moreover, factors that influence cell sensitivity to these drugs are mostly unknown. There is evidence that p53-deficient tumors or tumors with mutated ras could be highly responsive to Plk1 inhibition (Degenhardt et al. 2010; Luo et al. 2009) and that combined ablation of DNA damage response and Plk1 elevates cell death in vitro (Liu and Erikson 2003). Biomarker studies are needed for validation of target inhibition, optimization of administration route and prediction of responsive patients. Moreover, identification of the most beneficial combinations of Plk1 inhibitors and other chemotherapeutics will be important from a clinical perspective (McInnes and Wyatt 2011).

Aurora A inhibitors

Aurora A plays an essential role in centrosome maturation at G2. The kinase also regulates centrosome separation at prophase and the bipolar spindle assembly at prometaphase (Vader and Lens 2008). Dysregulation of Aurora A is associated with increased cancer susceptibility and induction of CIN (Ewart-Toland et al. 2003). Moreover, Aurora A is overexpressed or amplified in various cancers, and the high expression appears to be associated with poor patient

prognosis and high tumor grade (Jeng et al. 2004; Marumoto et al. 2005; Miyoshi et al. 2001). The excess of Aurora A has been proposed to induce cell transformation and cause tumor formation in nude mice (Zhou et al. 1998). However, additional genetic changes are probably needed to drive the tumorigenesis in cells overexpressing the kinase (Zhang et al. 2004). A plethora of different mechanisms may account for tumorigenic function of Aurora A overexpression in cells: SAC is overridden (Jiang et al. 2003) and cytokinesis is perturbed, which together can lead to the observed induction of tetraploidy (Jiang et al. 2003; Meraldi et al. 2002) and centrosome amplification (Meraldi et al. 2002).

Most Aurora kinase inhibitors target both Aurora A and B but with different efficiencies. In this chapter, we focus on the inhibitors that are more specific towards the Aurora A kinase. MLN8054, developed by Millennium Pharmaceuticals, is the first selective ATP-competitive small-molecule compound against the Aurora A activity (Manfredi et al. 2007). The drug-induced effects of MLN8054 have been extensively investigated in various cancer cell lines (Manfredi et al. 2007; Hoar et al. 2007). In the MLN8054-treated cell populations, the majority of cells exhibit spindle abnormalities and chromosome alignment defects which activate the SAC and induce a transient mitotic delay. Due to the induction of chromosome bridges and lagging chromosomes among other segregation defects, the daughter cells become aneuploid, which eventually increases cell death. The anti-tumor effects of MLN8054 have been confirmed in murine xenograft model (Manfredi et al. 2007), and the compound entered phase I trials for advanced solid tumors in 2005. However, due to the adverse effects on the central nervous system, the maximum tolerated concentration achieved in plasma was insufficient to kill tumor cells (Dees et al. 2011). MLN8237, an analogue of MLN8054, has an improved specificity, and at the moment several phase II trials on patients with solid tumors and haematological malignancies are being initiated (Kollareddy et al. 2012; Matulonis et al. 2012). Other Aurora A inhibitors in clinical trials include MK-5108 developed by Vertex Pharmaceuticals, ENMD-2076 from EntreMed Inc. and MP529 pharmacophore by SuperGen Inc. Recent reports show that MK-5108 stabilizes the disease as a single agent and delivers also a partial response when combined with docetaxel in patients with advanced solid tumors (Minton et al. 2010; Shimomura et al. 2010). ENMD-2076 has proceeded to phase II with ovarian cancer patients (Matulonis et al. 2013) and also holds a great promise for the treatment of acute myeloid leukaemia (AML) and multiple myeloma (MM) (How and Yee 2012; Zhang and Farag 2011). MP529 which belongs to pyrimido[4,5-b]indole class of compounds appears to be very potent and specific Aurora A drug in various cancer cell lines and also reduces tumor growth in xenograft model (http://www.healthtech.com/conferences_track_overview.aspx?id=77554&c=).

Despite the encouraging pre-clinical potency, the clinical efficacy of Aurora A inhibitors remains to be elucidated. Elevation of the mitotic index in the tumor has been considered to indicate target inhibition. However, additional biomarkers are likely required to measure other phenotypic drug effects such as mitotic slippage and post-mitotic cell cycle arrest (Chakravarty et al. 2011). One possible direct pharmacodynamic marker of Aurora A activity is the intracellular localization of the transforming acidic coiled-coil-containing protein 3 (TACC3) which is phosphorylated by Aurora A on Ser558, an event that localizes TACC3 to the spindle apparatus and centrosomes (LeRoy et al. 2007). MLN8054 inhibits Aurora A-mediated TACC3 phosphorylation, causing mislocalization of the protein. This was found to correlate with the loss of Aurora A autophosphorylation on Thr288, a commonly used pre-clinical marker for Aurora A activity. Moreover, determination of TACC3 localization may have technical advantages over measuring the Aurora A autophosphorylation in the clinical samples (LeRoy et al. 2007). Finally, there is evidence that spindle morphology and chromosome alignment together can reflect the clinical response to MLN8054 in skin and tumor biopsies (Chakravarty et al. 2011).

Aurora B as a drug target

Aurora B kinase functions as the catalytic subunit of the chromosomal passenger complex (CPC), whereas the other subunits INCENP, Borealin and Survivin contribute to overall activity, sub-cellular localization and function of the complex (Vader et al. 2006). Aurora B is involved in several key processes throughout mitosis (Vader and Lens 2008; Carmena and Earnshaw 2003; Vagnarelli and Earnshaw 2004), including chromosome condensation, sister chromatid cohesion, resolution of incorrect MT–KT attachments, SAC signalling and cytokinesis. Furthermore, Cenp-E and the SAC proteins BubR1 and Mad2 depend on Aurora B for their KT localization (Ditchfield et al. 2003). Overexpression of Aurora B has been detected in multiple human tumors of different tissue origin (Chieffi et al. 2006; Smith et al. 2005; Sorrentino et al. 2005; Zeng et al. 2007), and it correlates with genetic instability (Smith et al. 2005; Fraizer et al. 2004), higher tumor grade and/or poor patient prognosis in various cancers (Chieffi et al. 2006; Sorrentino et al. 2005; Zeng et al. 2007; Katayama et al. 1999; Kurai et al. 2005). A forced overexpression of Aurora B generates aneuploidy in several human cancer cell lines (Tatsuka et al. 1998), and Chinese hamster embryo cells with high exogenous Aurora B expression are able to form aggressive tumors in nude mice (Ota et al. 2002). Despite these studies, the role of kinase in tumorigenesis is not well established (Vader and Lens 2008). A forced Aurora B overexpression may have transforming potential alone (Ota et al. 2002) or together with H-Ras (Kanda et al. 2005). Cancer-associated mutations of the

gene have not been determined, and the locus is not found to be amplified (Smith et al. 2005). However, the fact that Aurora B is overexpressed in various cancers has encouraged the development of chemical inhibitors for therapeutic purposes. LMW compounds targeting Aurora B cause severe mitotic defects in cells: abrogation of SAC signalling, chromosome misalignment and failure of cytokinesis (Ditchfield et al. 2003; Hauf et al. 2003). Catastrophic mitosis leads to suppression of cell viability via pseudo G1 arrest or endoreduplication (Ditchfield et al. 2003; Hauf et al. 2003; Carvajal et al. 2006). Although not completely understood, lethality of Aurora B inhibition is thought to arise from severe polyploidization (Kaestner and Bastians 2010).

Aurora B specific inhibitors

Currently, Aurora B can be specifically targeted with at least four inhibitors; AZD1152 (Mortlock et al. 2007), ZM447439 (Ditchfield et al. 2003) and compound-677 (Nair et al. 2004) developed by AstraZeneca and hesperadin identified by J.-M. Peters and colleagues (Hauf et al. 2003). AZD1152 is a pro-drug which is metabolized into an active form, AZD1152-HQPA, in the plasma. The selectivity of the drug is 1,000-fold higher for Aurora B than for Aurora A (Walsby et al. 2008). The inhibitor induces apoptosis and suppresses tumor growth in models of colon, pancreatic, hepatocellular and lung cancer (Aihara et al. 2010; Azzariti et al. 2011; Wilkinson et al. 2007) as well as in models of haematological malignancies (Wilkinson et al. 2007; Evans et al. 2008; Yang et al. 2007). The effects on AML and acute lymphoblastic leukaemia (ALL) cell lines are synergistic with MT-depolymerizing agent vincristine and topoisomerase II inhibitor daunorubicin (Yang et al. 2007). In MM cell lines, AZD1152 is synergistic with dexamethasone (Evans et al. 2008). In colon carcinoma cell lines and mouse model of the disease, AZD1152 increases radiation-induced cell death, enhancing mitotic catastrophe, multinucleation and formation of micronuclei (Tao et al. 2008). The anti-tumorigenic effects are more pronounced in p53-deficient cells, proposing that a combination of DNA-damaging agents and Aurora B inhibition may have therapeutic advantages in a p53-defective background. In clinical studies, AZD1152 caused disease stabilization in patients with advanced solid tumors (Boss et al. 2011). Moreover, there are signs of therapeutic potential of AZD1152 in patients with advanced AML (Kollareddy et al. 2012; Lowenberg et al. 2011). ZM447439 (Ditchfield et al. 2003) is another compound that shows better selectivity against Aurora B over Aurora A (IC_{50} values of 50 and 1,000 nM, respectively) and is commonly used in cell-based studies and in vitro to explore the biological functions of the kinase. Hesperadin, which was discovered in cell assays as a compound inducing polyploidization (Hauf et al. 2003), targets Aurora B kinase in cells but also reduces the activity of AMPK, Lck, MKK1, MAPKAP-K1, CHK1 and PHK in vitro (Hauf et al. 2003). Much less is known about the compound-677; p53-deficient cells are sensitized to it and the inhibitor shows enhanced anti-proliferative effects when combined with other anti-cancer agents (Carvajal et al. 2006). Clinical data on compound-677 have not been published to date.

Dual Aurora inhibitors

Inhibitors that target both Aurora A and B kinases are in development by several parties. VX-680/MK-0457 (Harrington et al. 2004) and PHA-739358 (Carpinelli et al. 2007) are the most extensively characterized dual-Aurora inhibitors. VX-680 was originally identified as an in vitro kinase screen hit and was investigated in phase I clinical trials in patients with chronic myelogenous leukaemia (CML) and Philadelphia chromosome-positive ALL (Giles et al. 2007), but the trials were discontinued due to side effects on heart function. However, at least nine other LMW inhibitors of Aurora kinases have proceeded into clinical trials in patients with solid or haematological malignancies (Kollareddy et al. 2012). Three of the inhibitors, R763 (McLaughlin et al. 2010), PF-03814735 (Jani et al. 2010) and CYC116 (Wang et al. 2010), appear to be suitable also for oral administration and proceeded in phase I trials (Cheung et al. 2011). Danusertib (PHA-739358) (Fancelli et al. 2006) has proceeded into phase II trials for treatment of advanced solid tumors and CML (Kollareddy et al. 2012). Interestingly, besides inhibiting Aurora B, VX-680 and PHA-739358 also inhibit Bcr-Abl and therefore are considered as potential second-generation drugs for imatinib-resistant patients (Gontarewicz et al. 2008; Weisberg et al. 2007). In addition, a plethora of Aurora inhibitors are in pre-clinical development, and novel inhibitors of both natural and synthetic origin are still being identified (Schmidt and Bastians 2007; Kollareddy et al. 2012; Salmela et al. 2012; Salmela et al. 2009).

Determinants of the Aurora inhibition sensitivity

The sensitivity determinants of Aurora inhibition have been intensively studied but still are not well understood. Aurora kinase expression typically peaks in mitosis, and therefore it is thought that cell populations with high mitotic index may be more vulnerable for Aurora inhibition in comparison to the differentiated cells (Keen and Taylor 2009). There is a body of evidence that the p53 status can influence cell fate upon Aurora kinase inhibition (Ditchfield et al. 2003; Gizatullin et al. 2006; Margolis et al. 2003); typically p53-deficient cells become polyploid and undergo cell death when Aurora B is suppressed, which is in contrast to inhibitor-treated p53-proficient cells that arrest at pseudo-G1 phase (Ditchfield et al. 2003; Hauf et al. 2003; Harrington et al.

2004; Gizatullin et al. 2006). The pseudo-G1 arrest is in line with the notion that many Aurora inhibitors induce accumulation of p53 (Gizatullin et al. 2006; Dreier et al. 2009; Kaestner et al. 2009), which halts the cell cycle transition from G1 to S phase by inducing the expression of Cdk inhibitor p21. However, p53 may not fully prevent endoreduplication and may not arrest the cells immediately after the first erratic mitosis (Dreier et al. 2009). It has been shown that, in long-term cell cultures in the presence of ZM447439, some cell colonies emerge independent of the p53 status of the cell line, indicating that few cells in the populations are able to resume proliferation. Importantly, these cells are not resistant to the Aurora inhibitor, suggesting that other mechanisms allowed cells to evade the killing. Moreover, in clinics, these cells could possibly be targeted again by repeating the therapy regimen (Dreier et al. 2009). Predicting the cell fate in Aurora inhibitor-treated tumors based on the p53 status alone is altogether too simplistic. Results from a study in which a panel of cell lines with different p53 statuses was used suggest that inhibition of Aurora B can induce polyploidy independent of the p53 function (Nair et al. 2009).

Besides p53, p21 and retinoblastoma protein (Rb) are also important for the post-mitotic checkpoint and may influence the cells' response to Aurora inhibition. Supporting this notion, cell lines responded differently to Aurora inhibitors depending on their level and kinetics of p21 induction, inhibition of cyclin E-Cdk2 complex and the Rb phosphorylation status (Gizatullin et al. 2006). Accordingly, it was suggested that along p53 functionality the integrity of the p53-p21 pathway and the Rb status can also affect the drug response. On the other hand, induction of p53 or p21 does not necessarily correlate with the extent of polyploidy (Nair et al. 2009). In the same study, the authors found Rb Ser780 to be a substrate of Aurora B (Nair et al. 2009). It was observed that Rb hypophoshorylation upon Aurora inhibition was associated with induction of polyploidy, which led the authors to suggest that Aurora B-mediated Rb Ser780 phosphorylation works to prevent endoreduplication via regulating the post-mitotic checkpoint after an aberrant mitosis (Nair et al. 2009). Finally, determination of the Myc expression levels could be useful in predicting the cells' response to Aurora B inhibition (Yang et al. 2010) because the Myc-overexpressing tumors appear to depend on Aurora B for malignancy (den Hollander et al. 2010). In conclusion, data from several laboratories suggest that p53 is not the only determinant for the cellular outcome of Aurora B inhibition (Ditchfield et al. 2003; Gizatullin et al. 2006; Dreier et al. 2009; Kaestner et al. 2009), but p21, Rb and Myc are also contributing factors.

Clinical data indicate that novel mitosis-targeting drugs, including Aurora inhibitors, have anti-tumor potential, although weaker than the MT drugs (Manchado et al. 2012). The importance of the kinases in tumorigenesis is not well established, and their role during cancer formation may be only transient (Kollareddy et al. 2012). Moreover, due to the harmful effects of mitosis-targeting therapies on bone marrow, continuous treatment is impossible (Mitchison 2012). Duration of the treatment, penetrance of the drugs into the tumors, monitoring the treatment efficacy and identification of the most responsive patients are examples of the many issues that require further investigations before these inhibitors can be approved for clinical use (Keen and Taylor 2009). Also, it will be important to determine whether targeting a single or several Aurora kinases simultaneously is a more potent approach. Finally, investigations on possible synergies between Aurora kinase inhibitors and existing cancer drugs may prove valuable.

Hec1/NEK inhibitors

Hec1 (highly expressed in cancer 1, a.k.a Ndc80) is a member of a conserved Ndc80 complex comprised of Hec1, Nuf2, Spc24 and Spc25 (Tooley and Stukenberg 2011). The complex localizes to the outer KT plate where it is required for the formation of proper MT–KT attachments, chromosome congression and SAC function (Cheeseman et al. 2006; DeLuca et al. 2006; McCleland et al. 2003; Tooley et al. 2011; Wei et al. 2011). Hec1 is overexpressed in various human cancers (Wu et al. 2008). Furthermore, Hec1 depletion in tumor cell lines and in xenografts induces mitotic abnormalities and cell death (Gurzov and Izquierdo 2006; Li et al. 2007; Lin et al. 2006), which gives support for Hec1 inhibition as a potential therapeutic strategy. One interesting option to reach functional perturbation of a target protein is to prevent its association with an essential binding partner (allosteric inhibition). This is however a very challenging approach that requires information, e.g., about the high-resolution structures of the two proteins and the conformational changes that the interaction generates (Rudolph 2007). However, some success was achieved in the allosteric inhibition of Hec1 (Wu et al. 2008). Hec1–Nek2 kinase interaction has been shown to be important for Hec1 function in chromosome segregation (Chen et al. 2002) and stabilization of MT–KT attachments (Du et al. 2008). A yeast two-hybrid screen designed to identify LMW compounds preventing this interaction led to the discovery of INH1, a compound that binds to Hec1 and inhibits its interaction with Nek2 (Wu et al. 2008). Also, two INH1 analogues with improved potency have been synthesized (Qiu et al. 2009). Interestingly, INH1 treatment leads to reduced Nek2 protein levels. Reminiscent to depletion of Hec1 and Nek2 in cells, INH1 results in mitotic delay and induces a massive apoptosis after slippage from aberrant mitosis. In addition to the reduced viability of a panel of cancer cell lines, INH1 shows anti-tumor activity in a mouse xenograft model. However, whether the anti-tumor effects of INH1 in vivo are due to

disruption of the complex remains to be determined. The data also suggest that INH1 may possess cancer cell selectivity. Hec1–Nek2 interaction seems altogether a potential target for anti-cancer drug development, and clinical studies are awaited.

Histone deacetylase inhibitors

Genetic mutations can cause inactivation of tumor suppressors or activation of proto-oncogenes which can drive tumorigenesis. However, it has been known for years that epigenetic changes are also tightly associated with cancer formation (Yoo and Jones 2006). Epigenetic modifications include DNA methylation and acetylation, as well as methylation, ubiquitination, and glycosylation of histones which may, depending on the type and place of modification, activate or inactivate gene expression. Consequently, changes in epigenetic patterns can result in deregulated gene expression and genomic instability. Methylation and acetylation are reversible reactions, and therefore restoring the original pre-malignant epigenetic profile of cells is an attractive therapeutic possibility to treat cancer. Potential targets for such epigenetic drugs include DNA methyltransferases and histone deacetylases (HDACs). Currently, there are at least nine inhibitors of HDACs (HDACIs) from seven HDACI classes undergoing clinical trials, and two inhibitors, vorinostat (SAHA) and romidepsin, have gotten an FDA approval for treatment of cutaneous T cell lymphoma (Dell'Aversana et al. 2012). HDACIs possess anti-proliferative properties (Eot-Houllier et al. 2009) with some cancer cell specificity targeting both proliferating and non-proliferating tumor cells (Gabrielli et al. 2004; Warrener et al. 2003). A plethora of HDACI-induced mitotic defects have been described in vitro, including insufficient chromosome condensation, impaired KT assembly, mislocalization of the CPC, abnormal cytokinesis and polyploidy, structural spindle abnormalities and decreased Aurora A levels (Park et al. 2008). Moreover, various structurally diverse HDACIs suppress SAC activity (Warrener et al. 2003; Magnaghi-Jaulin et al. 2007; Stevens et al. 2008). Data from several laboratories suggest that both non-transcriptional changes, such as disruption of centromere structure and function, and prevention of histone deacetylation as well as transcriptional changes such as reduced expression of Aurora kinases, Plk1, survivin and cyclin B1 contribute to the formation of these mitotic abnormalities (Magnaghi-Jaulin et al. 2007; Noh et al. 2009; Taddei et al. 2001).

Given the multi-targeting nature of HDACIs, specific perturbation of mitotic processes may be difficult. However, HDACIs which can suppress the SAC activity and kill G2 checkpoint-deficient cancer cells without affecting normal cells are considered as promising therapeutic options. Importantly, induction of any mitotic anomalies by HDACIs in vivo remains to be investigated. Development of more selective inhibitors may decrease the side effects reported in clinical trials (Bruserud et al. 2007). Finally, there is evidence that HDACIs may increase the efficiency of certain anti-cancer agents such as proteasome inhibitors, CDK inhibitors and demethylating agents (Al-Janadi et al. 2008; Grant 2008).

Mps1 inhibitors

Mps1/TKK is a kinase which localizes at the KTs and whose activity peaks in mitosis (Stucke et al. 2002). Mps1 is essential for the correction of improper MT–KT attachments (Jelluma et al. 2008b) and SAC signalling (Stucke et al. 2002; Abrieu et al. 2001). The kinase is able to activate Aurora B via phosphorylation of Borealin (Jelluma et al. 2008b). On the other hand, there is evidence that Mps1 functions downstream of Aurora B, suggesting that the error correction and chromosome alignment functions of Mps1 may be independent of Aurora B (Hewitt et al. 2010; Santaguida et al. 2010). This variation in the results has been suggested to reflect the complex interactions between the two kinase pathways rather than linear interdependency (Lan and Cleveland 2010). It is possible that chromosome alignment depends on functions of both Mps1 and Aurora B on a common substrate, Cenp-E, whose phosphorylation by both kinases facilitates chromosome congression (Espeut et al. 2008; Kim et al. 2010). Mps1 has been shown to contribute to the SAC function in various manners, both in unperturbed cells and in cells treated with MT drugs (Stucke et al. 2002; Jelluma et al. 2008a; Tighe et al. 2008). Mps1 also works to stabilize p53 upon spindle damage, thereby promoting the activation of the G1 checkpoint and preventing genomic instability (Huang et al. 2009b). A few Mps1 substrates have been identified in vertebrates; one of them is the CPC subunit Borealin (Jelluma et al. 2008b). Also, BubR1 phosphorylation requires Mps1, but whether this is a direct reaction remains to be resolved (Huang et al. 2008). Cancer-associated frameshift mutations resulting in a premature stop of Mps1 synthesis are frequently found in gastric and colorectal tumors with microsatellite instability (Ahn et al. 2009), and overexpression of the protein is common in human tumors with CIN (Carter et al. 2006). Given that Mps1 activity is important for proper execution of mitosis and the protein is overexpressed in several cancers, pharmacological inhibition of the kinase may possess therapeutic value.

To date, at least half a dozen Mps1 inhibitors have been reported, one of which, cincreasin, is effective only in yeast (Dorer et al. 2005). SP600125 is the first reported inhibitor of mammalian Mps1 (Schmidt et al. 2005). Although originally identified as an inhibitor of JNK (Bennett et al. 2001), the compound induces defects in the SAC signalling that later have been shown to result from direct Mps1 inhibition

(Schmidt et al. 2005). In line with the SAC inhibition, BubR1 phosphorylation is reduced, and the kinase is mislocalized from KTs upon SP600125 treatment. The authors suggested that Mps1 activity is needed to recruit BubR1 to the KTs but is not necessary for Mad1 localization, which was confirmed later (Tighe et al. 2008). Mps1 activity has also been found essential for the KT recruitment of Mad2 (Tighe et al. 2008). SP600125, however, does not abolish Mad2 localization at KTs, raising a question on which drug target is responsible for the SAC inhibition (Tighe et al. 2008). In fact, the drug suppresses a wide range of kinases in vitro, most of which do not have any mitotic functions known to date (Schmidt et al. 2005). The structure of Mps1 catalytic domain alone and that in complex with SP600125 are available (Chu et al. 2008; Wang et al. 2009) for a structure-based design of more specific Mps1 inhibitors.

After the discovery of SP600125, other inhibitors of Mps1 have been characterized as, for example, AZ3146 (Hewitt et al. 2010), MPI-0479605 (Tardif et al. 2011), NMS-P715 (Colombo et al. 2010) and reversine (Santaguida et al. 2010), a compound originally identified as an Aurora B inhibitor (D'Alise et al. 2008). In several studies, chemical inhibition of Mps1 results in overriding the SAC, which leads to increased aneuploidy accompanied with loss of cell viability (Colombo et al. 2010; Kwiatkowski et al. 2012; Lan and Cleveland 2010; Tardif et al. 2011). MPI-0479605 and NMS-P715 possess anti-tumorigenic efficacy in xenograft models (Colombo et al. 2010; Tardif et al. 2011). MPI-0479605, however, also inhibits the growth of normal cells in vitro and causes side effects in mice, indicating lack of cancer cell specificity (Tardif et al. 2011). In contrast, NMS-P715 has only minor effects on the growth of normal cells, and its anti-tumorigenic doses are well tolerated in mice (Colombo et al. 2010). Mps1 altogether represents a potential anti-cancer drug target, and the experimental data from cell-based and xenograft assays justify further investigations on the Mps1 inhibitors.

Molecular mechanisms of anti-mitotic-induced cell death

Although cell death after perturbation of mitosis is extensively studied (for review, see Portugal et al. (2010)), the detailed mechanisms are not well understood (Schmidt and Bastians 2007; Gascoigne and Taylor 2008). The main question still remains: why does a prolongation of mitosis result in cell death? One possibility is that cell death ensues as a consequence of energy deprivation or, alternatively, as a result of increased sensitivity of DNA to damage during mitosis in the absence of the protecting nuclear envelope (Janssen and Medema 2011). The requirement of prolonged activation of SAC for the induction of cell death from mitosis has remained controversial. There is experimental evidence indicating that the activation status of SAC is important for the cells' sensitivity to MT drugs. This notion is supported by studies showing that loss of SAC protein function negatively regulates drug sensitivity (Masuda et al. 2003; Sudo et al. 2004; Tao 2005). However, great variation can be observed between the cell line responses to MT drugs and even between the individual cells within a "genetically identical" cell population (Gascoigne and Taylor 2008; Brito and Rieder 2009; Shi et al. 2008). For these reasons, it has been proposed that rather than the strength of SAC, differences in the expression levels and activity of cell death-associated proteins can be important determinants of drug sensitivity (Shi et al. 2008; Chin and Herbst 2006; Gascoigne and Taylor 2009). What is triggering the cell death from mitosis is poorly understood. Factors that control elimination of mitotically arrested cells include p53 that is induced during a prolonged M phase (Uetake and Sluder 2010). Cdk1 is also implicated in the maintenance of balance between pro- and anti-apoptosis signalling in M phase arrested cells; the prolonged activity of the kinase has a role in the inhibition of anti-apoptotic proteins Bcl-2 and Bcl-X_L and in the degradation of pro-survival Mcl1 and thereby in the promotion of activation of pro-apoptotic proteins Bax and Bak (Manchado et al. 2012; Terrano et al. 2010). Furthermore, Cdk1 inhibits caspase-9 (Allan and Clarke 2007) that becomes dephosphorylated upon prolonged mitosis, which may contribute to triggering of apoptosis.

The continued activity of SAC is not able to prevent the slow degradation of cyclin B1, which leads to gradual diminishment of the Cdk1 activity and eventually allows erroneous exit from M phase. A model of "two competing networks" states that during a mitotic arrest, the competition between cyclin B1 degradation and accumulation of apoptotic signals can determine the cell fate and direct the cells either towards death in mitosis or survival via mitotic slippage (Gascoigne and Taylor 2008). The presence of DNA damage and the status of gatekeeper genes such as p53 are likely also contributing factors. The pro-survival protein Mcl1 may possess a critical role in linking the length of mitotic arrest with the trigger of cell death induction (Harley et al. 2010; Matson and Stukenberg 2011; Wertz et al. 2011). According to the refined model, the relative rates of cyclin B and Mcl1 degradation may determine whether the cells that cannot satisfy the SAC will undergo mitotic slippage or apoptosis at M phase, respectively (Matson and Stukenberg 2011). The levels of Mcl1 first peak upon MT drug-induced mitotic arrest (Craig 2002) but then start to decrease as a result of proteasome-mediated degradation. This event is promoted by JNK, p38, CKII and CDK1 kinases and opposed by PP2A phosphatase activity (Wertz et al. 2011). Mcl1 degradation also requires Cdc20 and Apc3, whose depletion by RNAi stabilized Mcl1 in mitotic cells (Harley et al. 2010). Upon prolonged mitosis, Cdk1 enhances Mcl1 depletion and induction of cell death.

During a mitotic arrest, the kinase phosphorylates T92 on Mcl1, which may promote the dissociation of PP2A. This event may in turn promote the phosphorylation of Mcl1 on FBW7 degrons which are responsible for the association with FBW7, a substrate receptor of the ubiquitin ligase complex (Welcker and Clurman 2008) targeting Mcl1 to degradation (Inuzuka et al. 2011). FBW7 is also a tumor suppressor that is lost in various human cancers, often concomitantly with gain-of-function of Mcl1 in primary tumors (Wertz et al. 2011). Importantly, cell lines deficient of FBW7 show resistance to MT drugs and fail to undergo cell death in a Mcl1-dependent manner, which points to the existence of a mechanism that can allow the FBW7-deficient tumors to evade therapy-induced cell death (Wertz et al. 2011). These data suggest that determination of FBW7 and Mcl1 levels in tumors may have a diagnostic value as predictive markers of MT drug response (Wertz et al. 2011).

Mitotic slippage in the presence of MT drugs or SAC inhibitors can lead to tetraploidy via failure of cytokinesis. It has been proposed that a post-mitotic checkpoint functions in mammalian cells and responds to cellular damage such as cytoskeletal stress and DNA injury caused by drug treatments (Wong and Stearns 2005). The G1 checkpoint appears to co-operate with SAC (Suijkerbuijk and Kops 2008; Nair et al. 2009; Vogel et al. 2004) and is dependent on p53, Rb and p38/MAP kinase family (Wong and Stearns 2005; Vogel et al. 2004; Mikule et al. 2007). Although still controversial, the activation of G1 checkpoint has been reported to induce G1 arrest (senescence) in p53-proficient cells, whereas cells without functional p53 can continue cycling, endoreduplicate and give rise to aneuploid progeny (as reviewed in Ganem and Pellman (2007) and Rieder and Maiato (2004)). It is possible that cell death induced by anti-mitotics is a response to a range of aberrations caused by a prolonged M phase, such as accumulation of pro-apoptotic signals, morphological cell changes influencing, e.g., the cell adhesion signalling (Chrzanowska-Wodnicka and Burridge 1996; van Engeland et al. 1997) and interconnections between the centrosomes, spindle apparatus and actin cytoskeleton (van Engeland et al. 1997; Laster and Mackenzie 1996), as well as DNA damage induced via persistent chromosome condensation and/or chromatin injury during aberrant exit from mitosis (Dalton et al. 2007; Dalton and Yang 2009).

Slippage from mitosis without cell death is one of the mechanisms responsible for the development of drug resistance against M phase-arresting compounds (Manchado et al. 2012). For this reason, the extended mitotic arrest has been envisioned to enhance the treatment efficacy. In fact, recent evidence shows that prevention of cyclin B1 degradation by genetically ablating the APC/C activator Cdc20 is more efficient than paclitaxel or kinesin-5 inhibition in killing exit prone cancer cells (Huang et al. 2009a). Furthermore, introduction of non-degradable cyclin B1 to these cells led to similar effects (Huang et al. 2009a). These results support the hypothesis that inhibition of mitotic exit may possess therapeutic value as a novel MT-independent approach to target cell death-resistant cancer cells. Alternative possibilities to prevent cyclin B1 degradation and mitotic exit could include inhibition of other components of the APC/C or the proteasome function (Manchado et al. 2012). In the clinics, these novel cancer chemotherapeutics could potentially be used in combination with conventional anti-mitotics to target a wide range of tumors independently of their p53 or SAC statuses (Janssen and Medema 2011; Manchado et al. 2012; Huang et al. 2009a)

Conclusions and future outlook

Aneuploidy is implicated in tumorigenesis as both an initiator and promoter of cell malignancy. On the other hand, this common feature of tumor cells may also be utilized as a therapeutic intervention strategy in cases where the levels of induced aneuploidy exceed the cancer cells' tolerance for genomic imbalance. Aneuploidy is believed to be an integral mechanism on how traditional anti-mitotics induce cell death (Dalton and Yang 2009). Similarly, lethality caused by SAC inhibitors is thought to result from the generation of massive CIN. Currently available clinical data indicate that the novel anti-mitotics and SAC inhibitors do not cause adverse effects such as severe neuropathy which are associated with the use of MT drugs. However, these new compounds have not, in general, fulfilled the clinical expectations in terms of their anti-cancer efficacies as single agents (Chan et al. 2012; Manchado et al. 2012). The low efficacy may, among other reasons, mirror the longer doubling times of cells in human tumors compared to the cell models in vitro (Komlodi-Pasztor et al. 2012). Therefore, it may be that only a small fraction of the tumor cells are susceptible to the treatment with a mitosis-targeting drug.

Mitosis-specific inhibitors target all proliferating cells in the population and therefore cause adverse effects on rapidly dividing cells of the bone marrow. Furthermore, these inhibitors are not anticipated to target dormant tumor cells which can cause cancer recurrence. Due to these and other clinical limitations, the real therapeutic window of CIN induction remains to be determined. Elucidation of the mechanisms that enable tumor cells to adapt to low levels of aneuploidy is interesting from the point of view of drug discovery. It is not known, however, whether the adaptation processes are common to all aneuploid cells (Gordon et al. 2012). Aneuploidy causes stress to cancer cells; for instance, the cells have to cope with protein overload and protein misfolding and, as a response, need to be capable of activating protein unfolding and degradation cascades (Tang et al. 2011). Aneuploid cells also undergo metabolic alterations in response to numerical

chromosome alterations. Based on these findings, it may be possible to identify in the future new combination therapies where compounds that increase energetic or proteotoxic stress show synergistic effects with the anti-mitotics and thereby enable more selective targeting of cancer cells (Colombo et al. 2010; Manchado et al. 2012). Another potential therapeutic possibility for enhanced cancer cell selectivity is based on the inhibition of centrosomal clustering in the multipolar tumor cells (Kaestner and Bastians 2010; Kramer et al. 2011). Preventing the clustering of centrosomes and subsequent formation of bipolar spindles in the cancer cells could dramatically elevate the rate of aneuploidy and thus increase the vulnerability of the malignant cells. The target proteins and any clinical potential of these approaches remain to be proven.

To date, the clinical efficacy of next-generation mitosis-specific drugs as a single therapy form has been limited. In addition to testing new experimental anti-mitotic compounds, the researchers are becoming increasingly interested in finding and evaluating the clinical synergies between, e.g., chemotherapeutic DNA intercalators or precision anti-mitotics and classical cytotoxins. For instance, there is evidence that partial inhibition of the SAC may sensitize the cells to MT drugs (Janssen et al. 2009). This combination therapy may increase the rate of chromosome missegregation to the level which causes death of tumor cells and enable the use of lower MT drug concentrations which will alleviate neuropathy and other side effects that are associated with the functional perturbation of MTs (Kaestner and Bastians 2010). Moreover, combining anti-mitotics with compounds that inhibit repair of DNA damage (e.g. PARP inhibitors) or enhance degradation of anti-apoptotic proteins such as Mcl1 or inhibit mitotic exit (inhibitors of Cdc20 or APC/C) are approaches that deserve further attention (Matson and Stukenberg 2011; Dalton and Yang 2009; Huang et al. 2009a). Importantly, we lack knowledge on the long-term clinical effects of the combination therapies. Induction of aneuploidy or tetraploidy bares a risk for tumorigenesis in normal cells, although aneuploidy normally reduces proliferation potential, and diploid cells are selected for in the population. Aneuploidy-inducing treatments may also cause tumor relapse when a gene combination that promotes fitness is occasionally generated. The search for novel mitosis-targeting therapeutics will altogether be challenging, and more information about the pre-clinical and clinical efficacies of the existing anti-mitotics are required to assess their anti-cancer potencies in single-compound treatments as well as in drug cocktails.

References

Abrieu A, Magnaghi-Jaulin L, Kahana JA, Peter M, Castro A, Vigneron S, Lorca T, Cleveland DW, Labbe JC (2001) Mps1 is a kinetochore-associated kinase essential for the vertebrate mitotic checkpoint. Cell 106:83–93

Ahn CH, Kim YR, Kim SS, Yoo NJ, Lee SH (2009) Mutational analysis of TTK gene in gastric and colorectal cancers with microsatellite instability. Cancer Res Treat 41:224–228. doi:10.4143/crt.2009.41.4.224

Aihara A, Tanaka S, Yasen M et al (2010) The selective Aurora B kinase inhibitor AZD1152 as a novel treatment for hepatocellular carcinoma. J Hepatol 52:63–71. doi:10.1016/j.jhep.2009.10.013

Al-Janadi A, Chandana SR, Conley BA (2008) Histone deacetylation: an attractive target for cancer therapy? Drugs R D 9:369–383

Allan LA, Clarke PR (2007) Phosphorylation of caspase-9 by CDK1/cyclin B1 protects mitotic cells against apoptosis. Mol Cell 26:301–310. doi:10.1016/j.molcel.2007.03.019

Ashar HR, James L, Gray K, Carr D, Black S, Armstrong L, Bishop WR, Kirschmeier P (2000a) Farnesyl transferase inhibitors block the farnesylation of CENP-E and CENP-F and alter the association of CENP-E with the microtubules. J Biol Chem 275:30451–30457. doi:10.1074/jbc.M003469200

Ashar HR, Armstrong L, James LJ, Carr DM, Gray K, Taveras A, Doll RJ, Bishop WR, Kirschmeier PT (2000b) Biological effects and mechanism of action of farnesyl transferase inhibitors. Chem Res Toxicol 13:949–952

Azzariti A, Bocci G, Porcelli L et al (2011) Aurora B kinase inhibitor AZD1152: determinants of action and ability to enhance chemotherapeutics effectiveness in pancreatic and colon cancer. Br J Cancer 104:769–780. doi:10.1038/bjc.2011.21

Bakhoum SF, Danilova OV, Kaur P, Levy NB, Compton DA (2011) Chromosomal instability substantiates poor prognosis in patients with diffuse large B-cell lymphoma. Clin Cancer Res 17:7704–7711. doi:10.1158/1078-0432.CCR-11-2049

Beaupre DM, Cepero E, Obeng EA, Boise LH, Lichtenheld MG (2004) R115777 induces Ras-independent apoptosis of myeloma cells via multiple intrinsic pathways. Mol Cancer Ther 3:179–186

Bennett BL, Sasaki DT, Murray BW et al (2001) SP600125, an anthrapyrazolone inhibitor of Jun N-terminal kinase. Proc Natl Acad Sci U S A 98:13681–13686. doi:10.1073/pnas.251194298

Beria I, Bossi RT, Brasca MG et al (2011) NMS-P937, a 4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline derivative as potent and selective Polo-like kinase 1 inhibitor. Bioorg Med Chem Lett 21:2969–2974. doi:10.1016/j.bmcl.2011.03.054

Blagden SP, Molife LR, Seebaran A et al (2008) A phase I trial of ispinesib, a kinesin spindle protein inhibitor, with docetaxel in patients with advanced solid tumours. Br J Cancer 98:894–899. doi:10.1038/sj.bjc.6604264

Blangy A, Lane HA, d'Herin P, Harper M, Kress M, Nigg EA (1995) Phosphorylation by p34cdc2 regulates spindle association of human Eg5, a kinesin-related motor essential for bipolar spindle formation in vivo. Cell 83:1159–1169

Boss DS, Witteveen PO, van der Sar J, Lolkema MP, Voest EE, Stockman PK, Ataman O, Wilson D, Das S, Schellens JH (2011) Clinical evaluation of AZD1152, an i.v. inhibitor of Aurora B kinase, in patients with solid malignant tumors. Ann Oncol 22:431–437

Boveri T (1914) Zur Frage der Entstehung maligner tumoren. Fischer, Jena

Braun T, Fenaux P (2008) Farnesyltransferase inhibitors and their potential role in therapy for myelodysplastic syndromes and acute myeloid leukaemia. Br J Haematol 141:576–586. doi:10.1111/j.1365-2141.2008.07099.x

Brito DA, Rieder CL (2009) The ability to survive mitosis in the presence of microtubule poisons differs significantly between human nontransformed (RPE-1) and cancer (U2OS, HeLa) cells. Cell Motil Cytoskeleton 66:437–447. doi:10.1002/cm.20316

Bruserud O, Stapnes C, Ersvaer E, Gjertsen BT, Ryningen A (2007) Histone deacetylase inhibitors in cancer treatment: a review of the clinical toxicity and the modulation of gene expression in cancer cell. Curr Pharm Biotechnol 8:388–400

Carmena M, Earnshaw WC (2003) The cellular geography of aurora kinases. Nat Rev Mol Cell Biol 4:842–854. doi:10.1038/nrm1245

Carpinelli P, Ceruti R, Giorgini ML et al (2007) PHA-739358, a potent inhibitor of Aurora kinases with a selective target inhibition profile relevant to cancer. Mol Cancer Ther 6:3158–3168. doi:10.1158/1535-7163.MCT-07-0444

Carter SL, Eklund AC, Kohane IS, Harris LN, Szallasi Z (2006) A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. Nat Genet 38:1043–1048. doi:10.1038/ng1861

Carvajal RD, Tse A, Schwartz GK (2006) Aurora kinases: new targets for cancer therapy. Clin Cancer Res 12:6869–6875. doi:10.1158/1078-0432.CCR-06-1405

Chakravarty A, Shinde V, Tabernero J et al (2011) Phase I assessment of new mechanism-based pharmacodynamic biomarkers for MLN8054, a small-molecule inhibitor of Aurora A kinase. Cancer Res 71:675–685. doi:10.1158/0008-5472.CAN-10-1030

Chan KS, Koh CG, Li HY (2012) Mitosis-targeted anti-cancer therapies: where they stand. Cell Death Dis 3:e411. doi:10.1038/cddis.2012.148

Cheeseman IM, Chappie JS, Wilson-Kubalek EM, Desai A (2006) The conserved KMN network constitutes the core microtubule-binding site of the kinetochore. Cell 127:983–997. doi:10.1016/j.cell.2006.09.039

Chen Y, Riley DJ, Zheng L, Chen PL, Lee WH (2002) Phosphorylation of the mitotic regulator protein Hec1 by Nek2 kinase is essential for faithful chromosome segregation. J Biol Chem 277:49408–49416. doi:10.1074/jbc.M207069200

Cheung CH, Coumar MS, Chang JY, Hsieh HP (2011) Aurora kinase inhibitor patents and agents in clinical testing: an update (2009–10). Expert Opin Ther Pat 21:857–884. doi:10.1517/13543776.2011.574614

Chi YH, Jeang KT (2007) Aneuploidy and cancer. J Cell Biochem 102:531–538. doi:10.1002/jcb.21484

Chieffi P, Cozzolino L, Kisslinger A et al (2006) Aurora B expression directly correlates with prostate cancer malignancy and influence prostate cell proliferation. Prostate 66:326–333. doi:10.1002/pros.20345

Chin GM, Herbst R (2006) Induction of apoptosis by monastrol, an inhibitor of the mitotic kinesin Eg5, is independent of the spindle checkpoint. Mol Cancer Ther 5:2580–2591. doi:10.1158/1535-7163.MCT-06-0201

Choi CM, Seo KW, Jang SJ, Oh YM, Shim TS, Kim WS, Lee DS, Lee SD (2009) Chromosomal instability is a risk factor for poor prognosis of adenocarcinoma of the lung: fluorescence in situ hybridization analysis of paraffin-embedded tissue from Korean patients. Lung Cancer 64:66–70. doi:10.1016/j.lungcan.2008.07.016

Chrzanowska-Wodnicka M, Burridge K (1996) Rho-stimulated contractility drives the formation of stress fibers and focal adhesions. J Cell Biol 133:1403–1415

Chu ML, Chavas LM, Douglas KT, Eyers PA, Tabernero L (2008) Crystal structure of the catalytic domain of the mitotic checkpoint kinase Mps1 in complex with SP600125. J Biol Chem 283:21495–21500. doi:10.1074/jbc.M803026200

Chung V, Heath EI, Schelman WR, Johnson BM, Kirby LC, Lynch KM, Botbyl JD, Lampkin TA, Holen KD (2012) First-time-in-human study of GSK923295, a novel antimitotic inhibitor of centromere-associated protein E (CENP-E), in patients with refractory cancer. Cancer Chemother Pharmacol 69:733–741. doi:10.1007/s00280-011-1756-z

Colombo R, Caldarelli M, Mennecozzi M et al (2010) Targeting the mitotic checkpoint for cancer therapy with NMS-P715, an inhibitor of MPS1 kinase. Cancer Res 70:10255–10264. doi:10.1158/0008-5472.CAN-10-2101

Craig RW (2002) MCL1 provides a window on the role of the BCL2 family in cell proliferation, differentiation and tumorigenesis. Leukemia 16:444–454. doi:10.1038/sj.leu.2402416

Crespo NC, Ohkanda J, Yen TJ, Hamilton AD, Sebti SM (2001) The farnesyltransferase inhibitor, FTI-2153, blocks bipolar spindle formation and chromosome alignment and causes prometaphase accumulation during mitosis of human lung cancer cells. J Biol Chem 276:16161–16167. doi:10.1074/jbc.M006213200

Crespo NC, Delarue F, Ohkanda J, Carrico D, Hamilton AD, Sebti SM (2002) The farnesyltransferase inhibitor, FTI-2153, inhibits bipolar spindle formation during mitosis independently of transformation and Ras and p53 mutation status. Cell Death Differ 9:702–709. doi:10.1038/sj.cdd.4401023

Dai W, Wang Q, Liu T, Swamy M, Fang Y, Xie S, Mahmood R, Yang YM, Xu M, Rao CV (2004) Slippage of mitotic arrest and enhanced tumor development in mice with BubR1 haploinsufficiency. Cancer Res 64:440–445

D'Alise AM, Amabile G, Iovino M, Di Giorgio FP, Bartiromo M, Sessa F, Villa F, Musacchio A, Cortese R (2008) Reversine, a novel Aurora kinases inhibitor, inhibits colony formation of human acute myeloid leukemia cells. Mol Cancer Ther 7:1140–1149. doi:10.1158/1535-7163.MCT-07-2051

Dalton WB, Yang VW (2009) Role of prolonged mitotic checkpoint activation in the formation and treatment of cancer. Future Oncol 5:1363–1370. doi:10.2217/fon.09.118

Dalton WB, Nandan MO, Moore RT, Yang VW (2007) Human cancer cells commonly acquire DNA damage during mitotic arrest. Cancer Res 67:11487–11492. doi:10.1158/0008-5472.CAN-07-5162

Decordier I, Cundari E, Kirsch-Volders M (2008) Survival of aneuploid, micronucleated and/or polyploid cells: crosstalk between ploidy control and apoptosis. Mutat Res 651:30–39. doi:10.1016/j.mrgentox.2007.10.016

Dees EC, Infante JR, Cohen RB et al (2011) Phase 1 study of MLN8054, a selective inhibitor of Aurora A kinase in patients with advanced solid tumors. Cancer Chemother Pharmacol 67:945–954. doi:10.1007/s00280-010-1377-y

Degenhardt Y, Greshock J, Laquerre S et al (2010) Sensitivity of cancer cells to Plk1 inhibitor GSK461364A is associated with loss of p53 function and chromosome instability. Mol Cancer Ther 9:2079–2089. doi:10.1158/1535-7163.MCT-10-0095

Dell'Aversana C, Lepore I, Altucci L (2012) HDAC modulation and cell death in the clinic. Exp Cell Res 318:1229–1244. doi:10.1016/j.yexcr.2012.01.025

DeLuca JG, Gall WE, Ciferri C, Cimini D, Musacchio A, Salmon ED (2006) Kinetochore microtubule dynamics and attachment stability are regulated by Hec1. Cell 127:969–982. doi:10.1016/j.cell.2006.09.047

den Hollander J, Rimpi S, Doherty JR et al (2010) Aurora kinases A and B are up-regulated by Myc and are essential for maintenance of the malignant state. Blood 116:1498–1505. doi:10.1182/blood-2009-11-251074

Ding X, Yan F, Yao P et al (2010) Probing CENP-E function in chromosome dynamics using small molecule inhibitor syntelin. Cell Res 20:1386–1389. doi:10.1038/cr.2010.167

Ditchfield C, Johnson VL, Tighe A, Ellston R, Haworth C, Johnson T, Mortlock A, Keen N, Taylor SS (2003) Aurora B couples chromosome alignment with anaphase by targeting BubR1, Mad2, and Cenp-E to kinetochores. J Cell Biol 161:267–280. doi:10.1083/jcb.200208091

Dorer RK, Zhong S, Tallarico JA, Wong WH, Mitchison TJ, Murray AW (2005) A small-molecule inhibitor of Mps1 blocks the spindle-checkpoint response to a lack of tension on mitotic chromosomes. Curr Biol 15:1070–1076. doi:10.1016/j.cub.2005.05.020

Dreier MR, Grabovich AZ, Katusin JD, Taylor WR (2009) Short and long-term tumor cell responses to Aurora kinase inhibitors. Exp Cell Res 315:1085–1099. doi:10.1016/j.yexcr.2009.02.008

Du J, Cai X, Yao J et al (2008) The mitotic checkpoint kinase NEK2A regulates kinetochore microtubule attachment stability. Oncogene 27:4107–4114. doi:10.1038/onc.2008.34

Elia AE, Cantley LC, Yaffe MB (2003a) Proteomic screen finds pSer/pThr-binding domain localizing Plk1 to mitotic substrates. Science 299:1228–1231. doi:10.1126/science.1079079

Elia AE, Rellos P, Haire LF, Chao JW, Ivins FJ, Hoepker K, Mohammad D, Cantley LC, Smerdon SJ, Yaffe MB (2003b) The molecular basis for phosphodependent substrate targeting and regulation of Plks by the Polo-box domain. Cell 115:83–95

Ellis PM, Chu QS, Leighl N, Laurie SA, Fritsch H, Gaschler-Markefski B, Gyorffy S, Munzert G (2012) A phase I open-label dose-escalation study of intravenous BI 2536 together with pemetrexed in previously treated patients with non-small-cell lung cancer. Clin Lung Cancer 14:19–27. doi:10.1016/j.cllc.2012.04.003

Eot-Houllier G, Fulcrand G, Magnaghi-Jaulin L, Jaulin C (2009) Histone deacetylase inhibitors and genomic instability. Cancer Lett 274:169–176. doi:10.1016/j.canlet.2008.06.005

Espeut J, Gaussen A, Bieling P, Morin V, Prieto S, Fesquet D, Surrey T, Abrieu A (2008) Phosphorylation relieves autoinhibition of the kinetochore motor Cenp-E. Mol Cell 29:637–643. doi:10.1016/j.molcel.2008.01.004

Evans RP, Naber C, Steffler T, Checkland T, Maxwell CA, Keats JJ, Belch AR, Pilarski LM, Lai R, Reiman T (2008) The selective Aurora B kinase inhibitor AZD1152 is a potential new treatment for multiple myeloma. Br J Haematol 140:295–302. doi:10.1111/j.1365-2141.2007.06913.x

Ewart-Toland A, Briassouli P, de Koning JP et al (2003) Identification of Stk6/STK15 as a candidate low-penetrance tumor-susceptibility gene in mouse and human. Nat Genet 34:403–412. doi:10.1038/ng1220

Fancelli D, Moll J, Varasi M et al (2006) 1,4,5,6-Tetrahydropyrrolo[3,4-c]pyrazoles: identification of a potent Aurora kinase inhibitor with a favorable antitumor kinase inhibition profile. J Med Chem 49:7247–7251. doi:10.1021/jm060897w

Fraizer GC, Diaz MF, Lee IL, Grossman HB, Sen S (2004) Aurora-A/STK15/BTAK enhances chromosomal instability in bladder cancer cells. Int J Oncol 25:1631–1639

Gabrielli B, Warrener R, Burgess A, Beamish H (2004) Defining the chemotherapeutic targets of histone deacetylase inhibitors. Ann N Y Acad Sci 1030:627–635. doi:10.1196/annals.1329.073

Ganem NJ, Pellman D (2007) Limiting the proliferation of polyploid cells. Cell 131:437–440. doi:10.1016/j.cell.2007.10.024

Gao F, Ponte JF, Levy M et al (2009) hBub1 negatively regulates p53 mediated early cell death upon mitotic checkpoint activation. Cancer Biol Ther 8:548–556

Garcia-Saez I, Blot D, Kahn R, Kozielski F (2004) Crystallization and preliminary crystallographic analysis of the motor domain of human kinetochore-associated protein CENP-E using an automated crystallization procedure. Acta Crystallogr D: Biol Crystallogr 60:1158–1160. doi:10.1107/S0907444904009564

Gascoigne KE, Taylor SS (2008) Cancer cells display profound intra- and interline variation following prolonged exposure to antimitotic drugs. Cancer Cell 14:111–122. doi:10.1016/j.ccr.2008.07.002

Gascoigne KE, Taylor SS (2009) How do anti-mitotic drugs kill cancer cells? J Cell Sci 122:2579–2585. doi:10.1242/jcs.039719

Giles FJ, Cortes J, Jones D, Bergstrom D, Kantarjian H, Freedman SJ (2007) MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation. Blood 109:500–502. doi:10.1182/blood-2006-05-025049

Gilmartin AG, Bleam MR, Richter MC et al (2009) Distinct concentration-dependent effects of the Polo-like kinase 1-specific inhibitor GSK461364A, including differential effect on apoptosis. Cancer Res 69:6969–6977. doi:10.1158/0008-5472.CAN-09-0945

Gizatullin F, Yao Y, Kung V, Harding MW, Loda M, Shapiro GI (2006) The Aurora kinase inhibitor VX-680 induces endoreduplication and apoptosis preferentially in cells with compromised p53-dependent postmitotic checkpoint function. Cancer Res 66:7668–7677. doi:10.1158/0008-5472.CAN-05-3353

Gontarewicz A, Balabanov S, Keller G et al (2008) Simultaneous targeting of Aurora kinases and Bcr-Abl kinase by the small molecule inhibitor PHA-739358 is effective against imatinib-resistant BCR-ABL mutations including T315I. Blood 111:4355–4364. doi:10.1182/blood-2007-09-113175

Gordon DJ, Resio B, Pellman D (2012) Causes and consequences of aneuploidy in cancer. Nat Rev Genet 13:189–203. doi:10.1038/nrg3123

Grant S (2008) Is the focus moving toward a combination of targeted drugs? Best Pract Res Clin Haematol 21:629–637. doi:10.1016/j.beha.2008.08.003

Guo Y, Kim C, Ahmad S, Zhang J, Mao Y (2012) CENP-E-dependent BubR1 autophosphorylation enhances chromosome alignment and the mitotic checkpoint. J Cell Biol 198:205–217. doi:10.1083/jcb.201202152

Gurzov EN, Izquierdo M (2006) RNA interference against Hec1 inhibits tumor growth in vivo. Gene Ther 13:1–7. doi:10.1038/sj.gt.3302595

Hanisch A, Wehner A, Nigg EA, Sillje HH (2006) Different Plk1 functions show distinct dependencies on Polo-Box domain-mediated targeting. Mol Biol Cell 17:448–459. doi:10.1091/mbc.E05-08-0801

Hanks S, Coleman K, Reid S et al (2004) Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. Nat Genet 36:1159–1161. doi:10.1038/ng1449

Hardy PA, Zacharias H (2005) Reappraisal of the Hansemann–Boveri hypothesis on the origin of tumors. Cell Biol Int 29:983–992. doi:10.1016/j.cellbi.2005.10.001

Harley ME, Allan LA, Sanderson HS, Clarke PR (2010) Phosphorylation of Mcl-1 by CDK1-cyclin B1 initiates its Cdc20-dependent destruction during mitotic arrest. EMBO J 29:2407–2420. doi:10.1038/emboj.2010.112

Harousseau JL (2007) Farnesyltransferase inihibitors in hematologic malignancies. Blood Rev 21:173–182. doi:10.1016/j.blre.2006.12.001

Harrington EA, Bebbington D, Moore J et al (2004) VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. Nat Med 10:262–267. doi:10.1038/nm1003

Hasle H, Clemmensen IH, Mikkelsen M (2000) Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 355:165–169. doi:10.1016/S0140-6736(99)05264-2

Hauf S, Cole RW, LaTerra S, Zimmer C, Schnapp G, Walter R, Heckel A, van Meel J, Rieder CL, Peters JM (2003) The small molecule hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint. J Cell Biol 161:281–294. doi:10.1083/jcb.200208092

Heilig CE, Loffler H, Mahlknecht U, Janssen JW, Ho AD, Jauch A, Kramer A (2010) Chromosomal instability correlates with poor outcome in patients with myelodysplastic syndromes irrespectively of the cytogenetic risk group. J Cell Mol Med 14:895–902. doi:10.1111/j.1582-4934.2009.00905.x

Henderson MC, Shaw YJ, Wang H, Han H, Hurley LH, Flynn G, Dorr RT, Von Hoff DD (2009) UA62784, a novel inhibitor of centromere protein E kinesin-like protein. Mol Cancer Ther 8:36–44. doi:10.1158/1535-7163.MCT-08-0789

Hewitt L, Tighe A, Santaguida S, White AM, Jones CD, Musacchio A, Green S, Taylor SS (2010) Sustained Mps1 activity is required in mitosis to recruit O-Mad2 to the Mad1-C-Mad2 core complex. J Cell Biol 190:25–34. doi:10.1083/jcb.201002133

Hoar K, Chakravarty A, Rabino C, Wysong D, Bowman D, Roy N, Ecsedy JA (2007) MLN8054, a small-molecule inhibitor of Aurora A, causes spindle pole and chromosome congression defects leading to aneuploidy. Mol Cell Biol 27:4513–4525. doi:10.1128/MCB.02364-06

Holen KD, Belani CP, Wilding G et al (2011) A first in human study of SB-743921, a kinesin spindle protein inhibitor, to determine pharmacokinetics, biologic effects and establish a recommended phase II dose. Cancer Chemother Pharmacol 67:447–454. doi:10.1007/s00280-010-1346-5

Holland AJ, Cleveland DW (2012) Losing balance: the origin and impact of aneuploidy in cancer. EMBO Rep 13:501–514. doi:10.1038/embor.2012.55

How J, Yee K (2012) ENMD-2076 for hematological malignancies. Expert Opin Investig Drugs 21:717–732. doi:10.1517/13543784.2012.668882

Huang H, Hittle J, Zappacosta F, Annan RS, Hershko A, Yen TJ (2008) Phosphorylation sites in BubR1 that regulate kinetochore attachment, tension, and mitotic exit. J Cell Biol 183:667–680. doi:10.1083/jcb.200805163

Huang HC, Shi J, Orth JD, Mitchison TJ (2009a) Evidence that mitotic exit is a better cancer therapeutic target than spindle assembly. Cancer Cell 16:347–358. doi:10.1016/j.ccr.2009.08.020

Huang YF, Chang MD, Shieh SY (2009b) TTK/hMps1 mediates the p53-dependent postmitotic checkpoint by phosphorylating p53 at Thr18. Mol Cell Biol 29:2935–2944. doi:10.1128/MCB.01837-08

Hussein D, Taylor SS (2002) Farnesylation of Cenp-F is required for G2/M progression and degradation after mitosis. J Cell Sci 115:3403–3414

Huszar D, Theoclitou ME, Skolnik J, Herbst R (2009) Kinesin motor proteins as targets for cancer therapy. Cancer Metastasis Rev. doi:10.1007/s10555-009-9185-8

Ikui AE, Yang CP, Matsumoto T, Horwitz SB (2005) Low concentrations of taxol cause mitotic delay followed by premature dissociation of p55CDC from Mad2 and BubR1 and abrogation of the spindle checkpoint, leading to aneuploidy. Cell Cycle 4:1385–1388

Inuzuka H, Shaik S, Onoyama I et al (2011) SCF(FBW7) regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction. Nature 471:104–109. doi:10.1038/nature09732

Iwanaga Y, Chi YH, Miyazato A, Sheleg S, Haller K, Peloponese JM Jr, Li Y, Ward JM, Benezra R, Jeang KT (2007) Heterozygous deletion of mitotic arrest-deficient protein 1 (MAD1) increases the incidence of tumors in mice. Cancer Res 67:160–166. doi:10.1158/0008-5472.CAN-06-3326

Jallepalli PV, Lengauer C (2001) Chromosome segregation and cancer: cutting through the mystery. Nat Rev Cancer 1:109–117. doi:10.1038/35101065

Jani JP, Arcari J, Bernardo V et al (2010) PF-03814735, an orally bioavailable small molecule aurora kinase inhibitor for cancer therapy. Mol Cancer Ther 9:883–894. doi:10.1158/1535-7163.MCT-09-0915

Janssen A, Medema RH (2011) Mitosis as an anti-cancer target. Oncogene 30:2799–2809. doi:10.1038/onc.2011.30

Janssen A, Kops GJ, Medema RH (2009) Elevating the frequency of chromosome mis-segregation as a strategy to kill tumor cells. Proc Natl Acad Sci U S A 106:19108–19113. doi:10.1073/pnas.0904343106

Jeganathan K, Malureanu L, Baker DJ, Abraham SC, van Deursen JM (2007) Bub1 mediates cell death in response to chromosome missegregation and acts to suppress spontaneous tumorigenesis. J Cell Biol 179:255–267. doi:10.1083/jcb.200706015

Jelluma N, Brenkman AB, McLeod I, Yates JR 3rd, Cleveland DW, Medema RH, Kops GJ (2008a) Chromosomal instability by inefficient Mps1 auto-activation due to a weakened mitotic checkpoint and lagging chromosomes. PLoS One 3:e2415. doi:10.1371/journal.pone.0002415

Jelluma N, Brenkman AB, van den Broek NJ, Cruijsen CW, van Osch MH, Lens SM, Medema RH, Kops GJ (2008b) Mps1 phosphorylates Borealin to control Aurora B activity and chromosome alignment. Cell 132:233–246. doi:10.1016/j.cell.2007.11.046

Jeng YM, Peng SY, Lin CY, Hsu HC (2004) Overexpression and amplification of Aurora-A in hepatocellular carcinoma. Clin Cancer Res 10:2065–2071

Jiang Y, Zhang Y, Lees E, Seghezzi W (2003) AuroraA overexpression overrides the mitotic spindle checkpoint triggered by nocodazole, a microtubule destabilizer. Oncogene 22:8293–8301. doi:10.1038/sj.onc.1206873

Jones SF, Plummer ER, Burris HA, Razak AR, Meluch A, Bowen CJ, Williams DH, Hodge JP, Dar MM, Calvert AH (2006) Phase I study of ispinesib in combination with carboplatin in patients with advanced solid tumors. J Clin Oncol 24(18 Supplement):2027, ASCO Meeting Abstracts 5/17/2013 2013

Jordan MA, Wilson L (2004) Microtubules as a target for anticancer drugs. Nat Rev Cancer 4:253–265. doi:10.1038/nrc1317

Kaestner P, Bastians H (2010) Mitotic drug targets. J Cell Biochem 111:258–265. doi:10.1002/jcb.22721

Kaestner P, Stolz A, Bastians H (2009) Determinants for the efficiency of anticancer drugs targeting either Aurora-A or Aurora-B kinases in human colon carcinoma cells. Mol Cancer Ther 8:2046–2056. doi:10.1158/1535-7163.MCT-09-0323

Kanda A, Kawai H, Suto S, Kitajima S, Sato S, Takata T, Tatsuka M (2005) Aurora-B/AIM-1 kinase activity is involved in Ras-mediated cell transformation. Oncogene 24:7266–7272. doi:10.1038/sj.onc.1208884

Kapoor TM, Lampson MA, Hergert P, Cameron L, Cimini D, Salmon ED, McEwen BF, Khodjakov A (2006) Chromosomes can congress to the metaphase plate before biorientation. Science 311:388–391. doi:10.1126/science.1122142

Katayama H, Ota T, Jisaki F, Ueda Y, Tanaka T, Odashima S, Suzuki F, Terada Y, Tatsuka M (1999) Mitotic kinase expression and colorectal cancer progression. J Natl Cancer Inst 91:1160–1162

Keen N, Taylor S (2009) Mitotic drivers-inhibitors of the Aurora B kinase. Cancer Metastasis Rev. doi:10.1007/s10555-009-9184-9

Kim Y, Holland AJ, Lan W, Cleveland DW (2010) Aurora kinases and protein phosphatase 1 mediate chromosome congression through regulation of CENP-E. Cell 142:444–455. doi:10.1016/j.cell.2010.06.039

King RW (2008) When 2 + 2 = 5: the origins and fates of aneuploid and tetraploid cells. Biochim Biophys Acta 1786:4–14. doi:10.1016/j.bbcan.2008.07.007

Kohl NE, Mosser SD, deSolms SJ, Giuliani EA, Pompliano DL, Graham SL, Smith RL, Scolnick EM, Oliff A, Gibbs JB (1993) Selective inhibition of ras-dependent transformation by a farnesyltransferase inhibitor. Science 260:1934–1937

Kollareddy M, Zheleva D, Dzubak P, Brahmkshatriya PS, Lepsik M, Hajduch M (2012) Aurora kinase inhibitors: progress towards the clinic. Invest New Drugs. doi:10.1007/s10637-012-9798-6

Komlodi-Pasztor E, Sackett DL, Fojo AT (2012) Inhibitors targeting mitosis: tales of how great drugs against a promising target were brought down by a flawed rationale. Clin Cancer Res 18:51–63. doi:10.1158/1078-0432.CCR-11-0999

Kops GJ, Foltz DR, Cleveland DW (2004) Lethality to human cancer cells through massive chromosome loss by inhibition of the mitotic checkpoint. Proc Natl Acad Sci U S A 101:8699–8704. doi:10.1073/pnas.0401142101

Kops GJ, Weaver BA, Cleveland DW (2005) On the road to cancer: aneuploidy and the mitotic checkpoint. Nat Rev Cancer 5:773–785. doi:10.1038/nrc1714

Kramer A, Maier B, Bartek J (2011) Centrosome clustering and chromosomal (in)stability: a matter of life and death. Mol Oncol 5:324–335. doi:10.1016/j.molonc.2011.05.003

Kronenwett U, Huwendiek S, Ostring C, Portwood N, Roblick UJ, Pawitan Y, Alaiya A, Sennerstam R, Zetterberg A, Auer G (2004) Improved grading of breast adenocarcinomas based on genomic instability. Cancer Res 64:904–909

Kurai M, Shiozawa T, Shih HC, Miyamoto T, Feng YZ, Kashima H, Suzuki A, Konishi I (2005) Expression of Aurora kinases A and B in normal, hyperplastic, and malignant human endometrium: Aurora B as a predictor for poor prognosis in endometrial carcinoma. Hum Pathol 36:1281–1288. doi:10.1016/j.humpath.2005.09.014

Kwiatkowski N, Jelluma N, Filippakopoulos P et al (2010) Small-molecule kinase inhibitors provide insight into Mps1 cell cycle function. Nat Chem Biol 6:359–368. doi:10.1038/nchembio.345

Kwiatkowski N, Deng X, Wang J, Tan L, Villa F, Santaguida S, Huang HC, Mitchison T, Musacchio A, Gray N (2012) Selective aurora

kinase inhibitors identified using a taxol-induced checkpoint sensitivity screen. ACS Chem Biol 7:185–196. doi:10.1021/cb200305u

Lan W, Cleveland DW (2010) A chemical tool box defines mitotic and interphase roles for Mps1 kinase. J Cell Biol 190:21–24. doi:10.1083/jcb.201006080

Lansing TJ, McConnell RT, Duckett DR et al (2007) In vitro biological activity of a novel small-molecule inhibitor of Polo-like kinase 1. Mol Cancer Ther 6:450–459. doi:10.1158/1535-7163.MCT-06-0543

Lapenna S, Giordano A (2009) Cell cycle kinases as therapeutic targets for cancer. Nat Rev Drug Discov 8:547–566. doi:10.1038/nrd2907

Laster SM, Mackenzie JM Jr (1996) Bleb formation and F-actin distribution during mitosis and tumor necrosis factor-induced apoptosis. Microsc Res Tech 34:272–280

Lee KS, Grenfell TZ, Yarm FR, Erikson RL (1998) Mutation of the polo-box disrupts localization and mitotic functions of the mammalian polo kinase Plk. Proc Natl Acad Sci U S A 95:9301–9306

Lee RT, Beekman KE, Hussain M, Davis NB, Clark JI, Thomas SP, Nichols KF, Stadler WM (2008) A University of Chicago consortium phase II trial of SB-715992 in advanced renal cell cancer. Clin Genitourin Cancer 6:21–24. doi:10.3816/CGC.2008.n.003

Lee AJ, Endesfelder D, Rowan AJ et al (2011) Chromosomal instability confers intrinsic multidrug resistance. Cancer Res 71:1858–1870. doi:10.1158/0008-5472.CAN-10-3604

LeRoy PJ, Hunter JJ, Hoar KM, Burke KE, Shinde V, Ruan J, Bowman D, Galvin K, Ecsedy JA (2007) Localization of human TACC3 to mitotic spindles is mediated by phosphorylation on Ser558 by Aurora A: a novel pharmacodynamic method for measuring Aurora A activity. Cancer Res 67:5362–5370. doi:10.1158/0008-5472.CAN-07-0122

Li T, Sparano JA (2008) Farnesyl transferase inhibitors. Cancer Invest 26:653–661. doi:10.1080/07357900801971016

Li L, Yang L, Scudiero DA, Miller SA, Yu ZX, Stukenberg PT, Shoemaker RH, Kotin RM (2007) Development of recombinant adeno-associated virus vectors carrying small interfering RNA (shHec1)-mediated depletion of kinetochore Hec1 protein in tumor cells. Gene Ther 14:814–827. doi:10.1038/sj.gt.3302933

Lin YT, Chen Y, Wu G, Lee WH (2006) Hec1 sequentially recruits Zwint-1 and ZW10 to kinetochores for faithful chromosome segregation and spindle checkpoint control. Oncogene 25:6901–6914. doi:10.1038/sj.onc.1209687

Liu X, Erikson RL (2003) Polo-like kinase (Plk)1 depletion induces apoptosis in cancer cells. Proc Natl Acad Sci U S A 100:5789–5794. doi:10.1073/pnas.1031523100

Lowenberg B, Muus P, Ossenkoppele G et al (2011) Phase 1/2 study to assess the safety, efficacy, and pharmacokinetics of barasertib (AZD1152) in patients with advanced acute myeloid leukemia. Blood 118:6030–6036. doi:10.1182/blood-2011-07-366930

Luo L, Parrish CA, Nevins N et al (2007) ATP-competitive inhibitors of the mitotic kinesin KSP that function via an allosteric mechanism. Nat Chem Biol 3:722–726. doi:10.1038/nchembio.2007.34

Luo J, Emanuele MJ, Li D, Creighton CJ, Schlabach MR, Westbrook TF, Wong KK, Elledge SJ (2009) A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. Cell 137:835–848. doi:10.1016/j.cell.2009.05.006

Magnaghi-Jaulin L, Eot-Houllier G, Fulcrand G, Jaulin C (2007) Histone deacetylase inhibitors induce premature sister chromatid separation and override the mitotic spindle assembly checkpoint. Cancer Res 67:6360–6367. doi:10.1158/0008-5472.CAN-06-3012

Maliga Z, Mitchison TJ (2006) Small-molecule and mutational analysis of allosteric Eg5 inhibition by monastrol. BMC Chem Biol 6:2. doi:10.1186/1472-6769-6-2

Manchado E, Guillamot M, Malumbres M (2012) Killing cells by targeting mitosis. Cell Death Differ 19:369–377. doi:10.1038/cdd.2011.197

Manfredi MG, Ecsedy JA, Meetze KA et al (2007) Antitumor activity of MLN8054, an orally active small-molecule inhibitor of Aurora A kinase. Proc Natl Acad Sci U S A 104:4106–4111. doi:10.1073/pnas.0608798104

Margolis RL, Lohez OD, Andreassen PR (2003) G1 tetraploidy checkpoint and the suppression of tumorigenesis. J Cell Biochem 88:673–683. doi:10.1002/jcb.10411

Marumoto T, Zhang D, Saya H (2005) Aurora-A—a guardian of poles. Nat Rev Cancer 5:42–50. doi:10.1038/nrc1526

Masuda A, Maeno K, Nakagawa T, Saito H, Takahashi T (2003) Association between mitotic spindle checkpoint impairment and susceptibility to the induction of apoptosis by anti-microtubule agents in human lung cancers. Am J Pathol 163:1109–1116. doi:10.1016/S0002-9440(10)63470-0

Matson DR, Stukenberg PT (2011) Spindle poisons and cell fate: a tale of two pathways. Mol Interv 11:141–150. doi:10.1124/mi.11.2.12

Matulonis UA, Sharma S, Ghamande S et al (2012) Phase II study of MLN8237 (alisertib), an investigational Aurora A kinase inhibitor, in patients with platinum-resistant or -refractory epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Gynecol Oncol 127:63–69. doi:10.1016/j.ygyno.2012.06.040

Matulonis UA, Lee J, Lasonde B et al (2013) ENMD-2076, an oral inhibitor of angiogenic and proliferation kinases, has activity in recurrent, platinum resistant ovarian cancer. Eur J Cancer 49:121–131. doi:10.1016/j.ejca.2012.07.020

McCleland ML, Gardner RD, Kallio MJ, Daum JR, Gorbsky GJ, Burke DJ, Stukenberg PT (2003) The highly conserved Ndc80 complex is required for kinetochore assembly, chromosome congression, and spindle checkpoint activity. Genes Dev 17:101–114. doi:10.1101/gad.1040903

McInnes C, Wyatt MD (2011) PLK1 as an oncology target: current status and future potential. Drug Discov Today 16:619–625. doi:10.1016/j.drudis.2011.05.002

McInnes C, Mezna M, Fischer PM (2005) Progress in the discovery of Polo-like kinase inhibitors. Curr Top Med Chem 5:181–197

McLaughlin J, Markovtsov V, Li H et al (2010) Preclinical characterization of Aurora kinase inhibitor R763/AS703569 identified through an image-based phenotypic screen. J Cancer Res Clin Oncol 136:99–113. doi:10.1007/s00432-009-0641-1

Meraldi P, Honda R, Nigg EA (2002) Aurora-A overexpression reveals tetraploidization as a major route to centrosome amplification in p53−/− cells. EMBO J 21:483–492

Mikule K, Delaval B, Kaldis P, Jurcyzk A, Hergert P, Doxsey S (2007) Loss of centrosome integrity induces p38-p53-p21-dependent G1-S arrest. Nat Cell Biol 9:160–170

Minton SE, LoRusso P, Lockhart AC, Saif M, Krishnamurthi SS, Pickett-Gies CA, Wang Y, Guan S, Roben E, Stein MN (2010) A phase I study of MK-5108, an oral aurora A kinase inhibitor, in both monotherapy and in combination with docetaxel in patients with advanced solid tumors. J Clin Oncol 28(15):e13026, ASCO Meeting Abstracts 5/17/2013 2013

Mitchison TJ (2012) The proliferation rate paradox in antimitotic chemotherapy. Mol Biol Cell 23:1–6. doi:10.1091/mbc.E10-04-0335

Miyoshi Y, Iwao K, Egawa C, Noguchi S (2001) Association of centrosomal kinase STK15/BTAK mRNA expression with chromosomal instability in human breast cancers. Int J Cancer 92:370–373

Mortlock AA, Foote KM, Heron NM et al (2007) Discovery, synthesis, and in vivo activity of a new class of pyrazoloquinazolines as selective inhibitors of aurora B kinase. J Med Chem 50:2213–2224. doi:10.1021/jm061335f

Mross K, Frost A, Steinbild S, Hedbom S, Rentschler J, Kaiser R, Rouyrre N, Trommeshauser D, Hoesl CE, Munzert G (2008) Phase I dose escalation and pharmacokinetic study of BI 2536, a novel Polo-like kinase 1 inhibitor, in patients with advanced solid tumors. J Clin Oncol 26:5511–5517. doi:10.1200/JCO.2008.16.1547

Musacchio A, Salmon ED (2007) The spindle-assembly checkpoint in space and time. Nat Rev Mol Cell Biol 8:379–393. doi:10.1038/nrm2163

Nair J, Keen N, Schwartz G (2004) A novel aurora B kinase inhibitor with potent anticancer activity either as a single agent or in combination with chemotherapy [abstract 9568]. Proc Am Soc Clin Oncol 23:848

Nair JS, Ho AL, Tse AN, Coward J, Cheema H, Ambrosini G, Keen N, Schwartz GK (2009) Aurora B kinase regulates the postmitotic endoreduplication checkpoint via phosphorylation of the retinoblastoma protein at serine 780. Mol Biol Cell 20:2218–2228. doi:10.1091/mbc.E08-08-0885

Noh EJ, Lim DS, Jeong G, Lee JS (2009) An HDAC inhibitor, trichostatin A, induces a delay at G2/M transition, slippage of spindle checkpoint, and cell death in a transcription-dependent manner. Biochem Biophys Res Commun 378:326–331. doi:10.1016/j.bbrc.2008.11.057

Olmos D, Barker D, Sharma R et al (2011) Phase I study of GSK461364, a specific and competitive Polo-like kinase 1 inhibitor, in patients with advanced solid malignancies. Clin Cancer Res 17:3420–3430. doi:10.1158/1078-0432.CCR-10-2946

Ota T, Suto S, Katayama H, Han ZB, Suzuki F, Maeda M, Tanino M, Terada Y, Tatsuka M (2002) Increased mitotic phosphorylation of histone H3 attributable to AIM-1/Aurora-B overexpression contributes to chromosome number instability. Cancer Res 62:5168–5177

Panda D, Jordan MA, Chu KC, Wilson L (1996) Differential effects of vinblastine on polymerization and dynamics at opposite microtubule ends. J Biol Chem 271:29807–29812

Pandha H, Protheroe A, Wylie J, Parker C, Chambers J, Bell S, Munzert G (2008) An open label phase II trial of BI 2536, a novel Plk1 inhibitor, in patients with metastatic hormone refractory prostate cancer (HRPC). J Clin Oncol (26):(May 20 suppl;abstr 14547)

Paoletti A, Giocanti N, Favaudon V, Bornens M (1997) Pulse treatment of interphasic HeLa cells with nanomolar doses of docetaxel affects centrosome organization and leads to catastrophic exit of mitosis. J Cell Sci 110(Pt 19):2403–2415

Park JH, Jong HS, Kim SG, Jung Y, Lee KW, Lee JH, Kim DK, Bang YJ, Kim TY (2008) Inhibitors of histone deacetylases induce tumor-selective cytotoxicity through modulating Aurora-A kinase. J Mol Med (Berl) 86:117–128. doi:10.1007/s00109-007-0260-8

Parrish CA, Adams ND, Auger KR et al (2007) Novel ATP-competitive kinesin spindle protein inhibitors. J Med Chem 50:4939–4952. doi:10.1021/jm070435y

Portugal J, Mansilla S, Bataller M (2010) Mechanisms of drug-induced mitotic catastrophe in cancer cells. Curr Pharm Des 16:69–78

Purcell JW, Davis J, Reddy M et al (2010) Activity of the kinesin spindle protein inhibitor ispinesib (SB-715992) in models of breast cancer. Clin Cancer Res 16:566–576. doi:10.1158/1078-0432.CCR-09-1498

Putkey FR, Cramer T, Morphew MK, Silk AD, Johnson RS, McIntosh JR, Cleveland DW (2002) Unstable kinetochore–microtubule capture and chromosomal instability following deletion of CENP-E. Dev Cell 3:351–365

Qiu XL, Li G, Wu G, Zhu J, Zhou L, Chen PL, Chamberlin AR, Lee WH (2009) Synthesis and biological evaluation of a series of novel inhibitor of Nek2/Hec1 analogues. J Med Chem 52:1757–1767. doi:10.1021/jm8015969

Rath O, Kozielski F (2012) Kinesins and cancer. Nat Rev Cancer 12:527–539. doi:10.1038/nrc3310

Reindl W, Yuan J, Kramer A, Strebhardt K, Berg T (2008) Inhibition of polo-like kinase 1 by blocking polo-box domain-dependent protein–protein interactions. Chem Biol 15:459–466. doi:10.1016/j.chembiol.2008.03.013

Rickert KW, Schaber M, Torrent M et al (2008) Discovery and biochemical characterization of selective ATP competitive inhibitors of the human mitotic kinesin KSP. Arch Biochem Biophys 469:220–231. doi:10.1016/j.abb.2007.10.016

Rieder CL, Maiato H (2004) Stuck in division or passing through: what happens when cells cannot satisfy the spindle assembly checkpoint. Dev Cell 7:637–651. doi:10.1016/j.devcel.2004.09.002

Rudolph J (2007) Inhibiting transient protein-protein interactions: lessons from the Cdc25 protein tyrosine phosphatases. Nat Rev Cancer 7:202–211. doi:10.1038/nrc2087

Rudolph D, Steegmaier M, Hoffmann M, Grauert M, Baum A, Quant J, Haslinger C, Garin-Chesa P, Adolf GR (2009) BI 6727, a Polo-like kinase inhibitor with improved pharmacokinetic profile and broad antitumor activity. Clin Cancer Res 15:3094–3102. doi:10.1158/1078-0432.CCR-08-2445

Salmela AL, Pouwels J, Varis A, Kukkonen AM, Toivonen P, Halonen PK, Perala M, Kallioniemi O, Gorbsky GJ, Kallio MJ (2009) Dietary flavonoid fisetin induces a forced exit from mitosis by targeting the mitotic spindle checkpoint. Carcinogenesis 30:1032–1040. doi:10.1093/carcin/bgp101

Salmela AL, Pouwels J, Maki-Jouppila J, Kohonen P, Toivonen P, Kallio L, Kallio M (2012) Novel pyrimidine-2,4-diamine derivative suppresses the cell viability and spindle assembly checkpoint activity by targeting Aurora kinases. Carcinogenesis. doi:10.1093/carcin/bgs339

Santaguida S, Tighe A, D'Alise AM, Taylor SS, Musacchio A (2010) Dissecting the role of MPS1 in chromosome biorientation and the spindle checkpoint through the small molecule inhibitor reversine. J Cell Biol 190:73–87. doi:10.1083/jcb.201001036

Schafer-Hales K, Iaconelli J, Snyder JP, Prussia A, Nettles JH, El-Naggar A, Khuri FR, Giannakakou P, Marcus AI (2007) Farnesyl transferase inhibitors impair chromosomal maintenance in cell lines and human tumors by compromising CENP-E and CENP-F function. Mol Cancer Ther 6:1317–1328. doi:10.1158/1535-7163.MCT-06-0703

Schmidt M, Bastians H (2007) Mitotic drug targets and the development of novel anti-mitotic anticancer drugs. Drug Resist Updat 10:162–181. doi:10.1016/j.drup.2007.06.003

Schmidt M, Budirahardja Y, Klompmaker R, Medema RH (2005) Ablation of the spindle assembly checkpoint by a compound targeting Mps1. EMBO Rep 6:866–872. doi:10.1038/sj.embor.7400483

Schoffski P, Awada A, Dumez H, Gil T, Bartholomeus S, Wolter P, Taton M, Fritsch H, Glomb P, Munzert G (2012) A phase I, dose-escalation study of the novel Polo-like kinase inhibitor volasertib (BI 6727) in patients with advanced solid tumours. Eur J Cancer 48:179–186. doi:10.1016/j.ejca.2011.11.001

Sebastian M, Reck M, Waller CF et al (2010) The efficacy and safety of BI 2536, a novel Plk-1 inhibitor, in patients with stage IIIB/IV non-small cell lung cancer who had relapsed after, or failed, chemotherapy: results from an open-label, randomized phase II clinical trial. J Thorac Oncol 5:1060–1067. doi:10.1097/JTO.0b013e3181d95dd4

Seong YS, Kamijo K, Lee JS, Fernandez E, Kuriyama R, Miki T, Lee KS (2002) A spindle checkpoint arrest and a cytokinesis failure by the dominant-negative polo-box domain of Plk1 in U-2 OS cells. J Biol Chem 277:32282–32293. doi:10.1074/jbc.M202602200

Shi J, Orth JD, Mitchison T (2008) Cell type variation in responses to antimitotic drugs that target microtubules and kinesin-5. Cancer Res 68:3269–3276. doi:10.1158/0008-5472.CAN-07-6699

Shih IM, Zhou W, Goodman SN, Lengauer C, Kinzler KW, Vogelstein B (2001) Evidence that genetic instability occurs at an early stage of colorectal tumorigenesis. Cancer Res 61:818–822

Shimomura T, Hasako S, Nakatsuru Y et al (2010) MK-5108, a highly selective Aurora-A kinase inhibitor, shows antitumor activity alone and in combination with docetaxel. Mol Cancer Ther 9:157–166. doi:10.1158/1535-7163.MCT-09-0609

Smith MR, Wilson ML, Hamanaka R, Chase D, Kung H, Longo DL, Ferris DK (1997) Malignant transformation of mammalian cells initiated by constitutive expression of the Polo-like kinase. Biochem Biophys Res Commun 234:397–405

Smith SL, Bowers NL, Betticher DC, Gautschi O, Ratschiller D, Hoban PR, Booton R, Santibanez-Koref MF, Heighway J (2005) Overexpression of aurora B kinase (AURKB) in primary non-small cell lung carcinoma is frequent, generally driven from one allele, and correlates with the level of genetic instability. Br J Cancer 93:719–729. doi:10.1038/sj.bjc.6602779

Song SY, Meszoely IM, Coffey RJ, Pietenpol JA, Leach SD (2000) K-Ras-independent effects of the farnesyl transferase inhibitor L-744,832 on cyclin B1/Cdc2 kinase activity, G2/M cell cycle progression and apoptosis in human pancreatic ductal adenocarcinoma cells. Neoplasia 2:261–272

Sorrentino R, Libertini S, Pallante PL et al (2005) Aurora B overexpression associates with the thyroid carcinoma undifferentiated phenotype and is required for thyroid carcinoma cell proliferation. J Clin Endocrinol Metab 90:928–935. doi:10.1210/jc.2004-1518

Sotillo R, Schvartzman JM, Socci ND, Benezra R (2010) Mad2-induced chromosome instability leads to lung tumour relapse after oncogene withdrawal. Nature 464:436–440. doi:10.1038/nature08803

Souid AK, Dubowy RL, Ingle AM, Conlan MG, Sun J, Blaney SM, Adamson PC (2010) A pediatric phase I trial and pharmacokinetic study of ispinesib: a Children's Oncology Group Phase I Consortium study. Pediatr Blood Cancer 55:1323–1328. doi:10.1002/pbc.22609

Spankuch B, Heim S, Kurunci-Csacsko E, Lindenau C, Yuan J, Kaufmann M, Strebhardt K (2006) Down-regulation of Polo-like kinase 1 elevates drug sensitivity of breast cancer cells in vitro and in vivo. Cancer Res 66:5836–5846. doi:10.1158/0008-5472.CAN-06-0343

Spankuch B, Kurunci-Csacsko E, Kaufmann M, Strebhardt K (2007) Rational combinations of siRNAs targeting Plk1 with breast cancer drugs. Oncogene 26:5793–5807. doi:10.1038/sj.onc.1210355

Spankuch-Schmitt B, Bereiter-Hahn J, Kaufmann M, Strebhardt K (2002) Effect of RNA silencing of Polo-like kinase-1 (PLK1) on apoptosis and spindle formation in human cancer cells. J Natl Cancer Inst 94:1863–1877

Steegmaier M, Hoffmann M, Baum A et al (2007) BI 2536, a potent and selective inhibitor of Polo-like kinase 1, inhibits tumor growth in vivo. Curr Biol 17:316–322. doi:10.1016/j.cub.2006.12.037

Stevens FE, Beamish H, Warrener R, Gabrielli B (2008) Histone deacetylase inhibitors induce mitotic slippage. Oncogene 27:1345–1354. doi:10.1038/sj.onc.1210779

Stolz A, Vogel C, Schneider V, Ertych N, Kienitz A, Yu H, Bastians H (2009) Pharmacologic abrogation of the mitotic spindle checkpoint by an indolocarbazole discovered by cellular screening efficiently kills cancer cells. Cancer Res 69:3874–3883. doi:10.1158/0008-5472.CAN-08-3597

Strebhardt K, Ullrich A (2006) Targeting Polo-like kinase 1 for cancer therapy. Nat Rev Cancer 6:321–330. doi:10.1038/nrc1841

Stucke VM, Sillje HH, Arnaud L, Nigg EA (2002) Human Mps1 kinase is required for the spindle assembly checkpoint but not for centrosome duplication. EMBO J 21:1723–1732. doi:10.1093/emboj/21.7.1723

Sudo T, Nitta M, Saya H, Ueno NT (2004) Dependence of paclitaxel sensitivity on a functional spindle assembly checkpoint. Cancer Res 64:2502–2508

Suijkerbuijk SJ, Kops GJ (2008) Preventing aneuploidy: the contribution of mitotic checkpoint proteins. Biochim Biophys Acta 1786:24–31. doi:10.1016/j.bbcan.2008.04.001

Suijkerbuijk SJ, van Osch MH, Bos FL, Hanks S, Rahman N, Kops GJ (2010) Molecular causes for BUBR1 dysfunction in the human cancer predisposition syndrome mosaic variegated aneuploidy. Cancer Res 70:4891–4900. doi:10.1158/0008-5472.CAN-09-4319

Swanton C, Nicke B, Schuett M et al (2009) Chromosomal instability determines taxane response. Proc Natl Acad Sci U S A 106:8671–8676. doi:10.1073/pnas.0811835106

Taddei A, Maison C, Roche D, Almouzni G (2001) Reversible disruption of pericentric heterochromatin and centromere function by inhibiting deacetylases. Nat Cell Biol 3:114–120. doi:10.1038/35055010

Takai N, Hamanaka R, Yoshimatsu J, Miyakawa I (2005) Polo-like kinases (Plks) and cancer. Oncogene 24:287–291. doi:10.1038/sj.onc.1208272

Tang YC, Williams BR, Siegel JJ, Amon A (2011) Identification of aneuploidy-selective antiproliferation compounds. Cell 144:499–512. doi:10.1016/j.cell.2011.01.017

Tanudji M, Shoemaker J, L'Italien L, Russell L, Chin G, Schebye XM (2004) Gene silencing of CENP-E by small interfering RNA in HeLa cells leads to missegregation of chromosomes after a mitotic delay. Mol Biol Cell 15:3771–3781. doi:10.1091/mbc.E03-07-0482

Tao W (2005) The mitotic checkpoint in cancer therapy. Cell Cycle 4:1495–1499

Tao Y, Zhang P, Girdler F, Frascogna V, Castedo M, Bourhis J, Kroemer G, Deutsch E (2008) Enhancement of radiation response in p53-deficient cancer cells by the Aurora-B kinase inhibitor AZD1152. Oncogene 27:3244–3255. doi:10.1038/sj.onc.1210990

Tardif KD, Rogers A, Cassiano J et al (2011) Characterization of the cellular and antitumor effects of MPI-0479605, a small-molecule inhibitor of the mitotic kinase Mps1. Mol Cancer Ther 10:2267–2275. doi:10.1158/1535-7163.MCT-11-0453

Tatsuka M, Katayama H, Ota T, Tanaka T, Odashima S, Suzuki F, Terada Y (1998) Multinuclearity and increased ploidy caused by overexpression of the aurora- and Ipl1-like midbody-associated protein mitotic kinase in human cancer cells. Cancer Res 58:4811–4816

Tcherniuk S, van Lis R, Kozielski F, Skoufias DA (2010) Mutations in the human kinesin Eg5 that confer resistance to monastrol and *S*-trityl-L-cysteine in tumor derived cell lines. Biochem Pharmacol 79:864–872. doi:10.1016/j.bcp.2009.11.001

Terrano DT, Upreti M, Chambers TC (2010) Cyclin-dependent kinase 1-mediated Bcl-xL/Bcl-2 phosphorylation acts as a functional link coupling mitotic arrest and apoptosis. Mol Cell Biol 30:640–656. doi:10.1128/MCB.00882-09

Thompson SL, Compton DA (2008) Examining the link between chromosomal instability and aneuploidy in human cells. J Cell Biol 180:665–672. doi:10.1083/jcb.200712029

Tighe A, Staples O, Taylor S (2008) Mps1 kinase activity restrains anaphase during an unperturbed mitosis and targets Mad2 to kinetochores. J Cell Biol 181:893–901. doi:10.1083/jcb.200712028

Tooley J, Stukenberg PT (2011) The Ndc80 complex: integrating the kinetochore's many movements. Chromosome Res 19:377–391. doi:10.1007/s10577-010-9180-5

Tooley JG, Miller SA, Stukenberg PT (2011) The Ndc80 complex uses a tripartite attachment point to couple microtubule depolymerization to chromosome movement. Mol Biol Cell 22:1217–1226. doi:10.1091/mbc.E10-07-0626

Uetake Y, Sluder G (2010) Prolonged prometaphase blocks daughter cell proliferation despite normal completion of mitosis. Curr Biol 20:1666–1671. doi:10.1016/j.cub.2010.08.018

Vader G, Lens SM (2008) The Aurora kinase family in cell division and cancer. Biochim Biophys Acta 1786:60–72. doi:10.1016/j.bbcan.2008.07.003

Vader G, Medema RH, Lens SM (2006) The chromosomal passenger complex: guiding Aurora-B through mitosis. J Cell Biol 173:833–837. doi:10.1083/jcb.200604032

Vagnarelli P, Earnshaw WC (2004) Chromosomal passengers: the four-dimensional regulation of mitotic events. Chromosoma 113:211–222. doi:10.1007/s00412-004-0307-3

van Engeland M, Kuijpers HJ, Ramaekers FC, Reutelingsperger CP, Schutte B (1997) Plasma membrane alterations and cytoskeletal changes in apoptosis. Exp Cell Res 235:421–430. doi:10.1006/excr.1997.3738

Vogel C, Kienitz A, Hofmann I, Muller R, Bastians H (2004) Crosstalk of the mitotic spindle assembly checkpoint with p53 to prevent polyploidy. Oncogene 23:6845–6853. doi:10.1038/sj.onc.1207860

Vose JM, Friedberg JW, Waller EK, Cheson BD, Juvvigunta V, Fritsch H, Petit C, Munzert G, Younes A (2012) The Plk1 inhibitor BI 2536 in patients with refractory or relapsed non-Hodgkin

lymphoma: a phase I, open-label, single dose-escalation study. Leuk Lymphoma. doi:10.3109/10428194.2012.729833
Walsby E, Walsh V, Pepper C, Burnett A, Mills K (2008) Effects of the aurora kinase inhibitors AZD1152-HQPA and ZM447439 on growth arrest and polyploidy in acute myeloid leukemia cell lines and primary blasts. Haematologica 93:662–669. doi:10.3324/haematol.12148
Wang W, Yang Y, Gao Y et al (2009) Structural and mechanistic insights into Mps1 kinase activation. J Cell Mol Med 13:1679–1694. doi:10.1111/j.1582-4934.2008.00605.x
Wang S, Midgley CA, Scaerou F et al (2010) Discovery of *N*-phenyl-4-(thiazol-5-yl)pyrimidin-2-amine aurora kinase inhibitors. J Med Chem 53:4367–4378. doi:10.1021/jm901913s
Warrener R, Beamish H, Burgess A, Waterhouse NJ, Giles N, Fairlie D, Gabrielli B (2003) Tumor cell-selective cytotoxicity by targeting cell cycle checkpoints. FASEB J 17:1550–1552. doi:10.1096/fj.02-1003fje
Watanabe N, Sekine T, Takagi M, Iwasaki J, Imamoto N, Kawasaki H, Osada H (2009) Deficiency in chromosome congression by the inhibition of Plk1 polo box domain-dependent recognition. J Biol Chem 284:2344–2353. doi:10.1074/jbc.M805308200
Weaver BA, Cleveland DW (2007) Aneuploidy: instigator and inhibitor of tumorigenesis. Cancer Res 67:10103–10105. doi:10.1158/0008-5472.CAN-07-2266
Weaver BA, Cleveland DW (2008) The aneuploidy paradox in cell growth and tumorigenesis. Cancer Cell 14:431–433. doi:10.1016/j.ccr.2008.11.011
Weaver BA, Bonday ZQ, Putkey FR, Kops GJ, Silk AD, Cleveland DW (2003) Centromere-associated protein-E is essential for the mammalian mitotic checkpoint to prevent aneuploidy due to single chromosome loss. J Cell Biol 162:551–563. doi:10.1083/jcb.200303167
Weaver BA, Silk AD, Montagna C, Verdier-Pinard P, Cleveland DW (2007) Aneuploidy acts both oncogenically and as a tumor suppressor. Cancer Cell 11:25–36. doi:10.1016/j.ccr.2006.12.003
Wei R, Ngo B, Wu G, Lee WH (2011) Phosphorylation of the Ndc80 complex protein, HEC1, by Nek2 kinase modulates chromosome alignment and signaling of the spindle assembly checkpoint. Mol Biol Cell 22:3584–3594. doi:10.1091/mbc.E11-01-0012
Weisberg E, Manley PW, Cowan-Jacob SW, Hochhaus A, Griffin JD (2007) Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukaemia. Nat Rev Cancer 7:345–356. doi:10.1038/nrc2126
Welcker M, Clurman BE (2008) FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer 8:83–93. doi:10.1038/nrc2290
Wertz IE, Kusam S, Lam C et al (2011) Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. Nature 471:110–114. doi:10.1038/nature09779
Wilkinson RW, Odedra R, Heaton SP et al (2007) AZD1152, a selective inhibitor of Aurora B kinase, inhibits human tumor xenograft growth by inducing apoptosis. Clin Cancer Res 13:3682–3688. doi:10.1158/1078-0432.CCR-06-2979
Wong C, Stearns T (2005) Mammalian cells lack checkpoints for tetraploidy, aberrant centrosome number, and cytokinesis failure. BMC Cell Biol 6:6. doi:10.1186/1471-2121-6-6
Wood KW, Chua P, Sutton D, Jackson JR (2008) Centromere-associated protein E: a motor that puts the brakes on the mitotic checkpoint. Clin Cancer Res 14:7588–7592. doi:10.1158/1078-0432.CCR-07-4443
Wood KW, Lad L, Luo L et al (2010) Antitumor activity of an allosteric inhibitor of centromere-associated protein-E. Proc Natl Acad Sci U S A 107:5839–5844. doi:10.1073/pnas.0915068107
Wu G, Qiu XL, Zhou L, Zhu J, Chamberlin R, Lau J, Chen PL, Lee WH (2008) Small molecule targeting the Hec1/Nek2 mitotic pathway suppresses tumor cell growth in culture and in animal. Cancer Res 68:8393–8399. doi:10.1158/0008-5472.CAN-08-1915
Yamada HY, Gorbsky GJ (2006) Spindle checkpoint function and cellular sensitivity to antimitotic drugs. Mol Cancer Ther 5:2963–2969. doi:10.1158/1535-7163.MCT-06-0319
Yang J, Ikezoe T, Nishioka C et al (2007) AZD1152, a novel and selective aurora B kinase inhibitor, induces growth arrest, apoptosis, and sensitization for tubulin depolymerizing agent or topoisomerase II inhibitor in human acute leukemia cells in vitro and in vivo. Blood 110:2034–2040. doi:10.1182/blood-2007-02-073700
Yang D, Liu H, Goga A, Kim S, Yuneva M, Bishop JM (2010) Therapeutic potential of a synthetic lethal interaction between the MYC proto-oncogene and inhibition of aurora-B kinase. Proc Natl Acad Sci U S A 107:13836–13841. doi:10.1073/pnas.1008366107
Yao X, Abrieu A, Zheng Y, Sullivan KF, Cleveland DW (2000) CENP-E forms a link between attachment of spindle microtubules to kinetochores and the mitotic checkpoint. Nat Cell Biol 2:484–491. doi:10.1038/35019518
Yen TJ, Li G, Schaar BT, Szilak I, Cleveland DW (1992) CENP-E is a putative kinetochore motor that accumulates just before mitosis. Nature 359:536–539. doi:10.1038/359536a0
Yoo CB, Jones PA (2006) Epigenetic therapy of cancer: past, present and future. Nat Rev Drug Discov 5:37–50. doi:10.1038/nrd1930
Yvon AM, Wadsworth P, Jordan MA (1999) Taxol suppresses dynamics of individual microtubules in living human tumor cells. Mol Biol Cell 10:947–959
Zeng WF, Navaratne K, Prayson RA, Weil RJ (2007) Aurora B expression correlates with aggressive behaviour in glioblastoma multiforme. J Clin Pathol 60:218–221. doi:10.1136/jcp.2006.036806
Zhang S, Farag SS (2011) From cell biology to therapy: ENMD-2076 in the treatment of multiple myeloma. Expert Opin Investig Drugs 20:1015–1028. doi:10.1517/13543784.2011.584869
Zhang D, Hirota T, Marumoto T et al (2004) Cre-loxP-controlled periodic Aurora-A overexpression induces mitotic abnormalities and hyperplasia in mammary glands of mouse models. Oncogene 23:8720–8730. doi:10.1038/sj.onc.1208153
Zhou H, Kuang J, Zhong L, Kuo WL, Gray JW, Sahin A, Brinkley BR, Sen S (1998) Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat Genet 20:189–193. doi:10.1038/2496
Zich J, Hardwick KG (2010) Getting down to the phosphorylated 'nuts and bolts' of spindle checkpoint signalling. Trends Biochem Sci 35:18–27. doi:10.1016/j.tibs.2009.09.002