JCB Journal of Cell Biology

INSIDE LOOK

Anti-mitotic therapies in cancer

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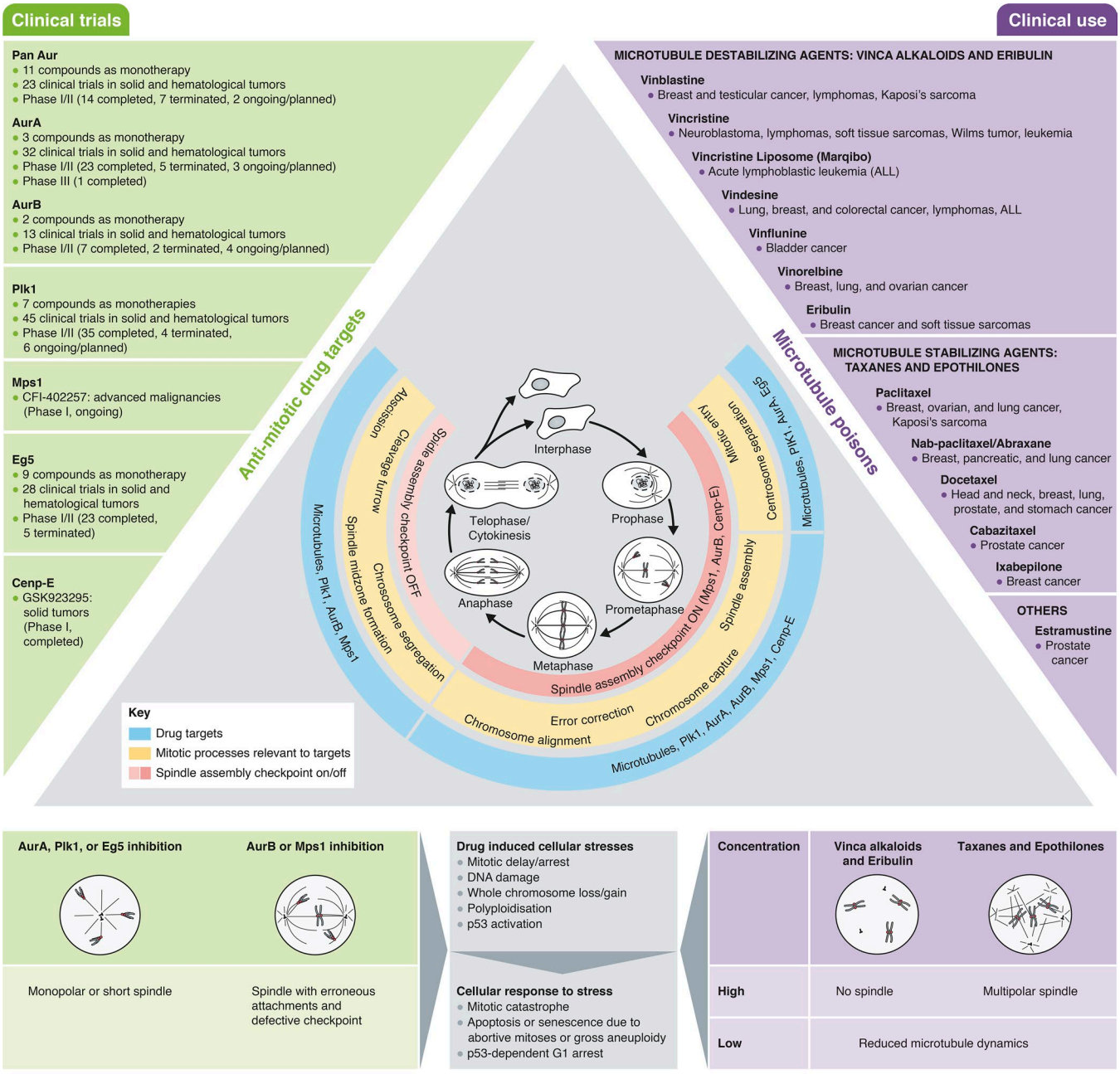

Artwork by Neil Smith (neil@neilsmithillustration.co.uk).

https://doi.org/10.1083/jcb.201808077

Chronic cellular proliferation is a hallmark of cancer, and therefore therapies targeting key pathways that drive and execute cell division have been a major research goal. The somatic cell division cycle culminates in mitosis, when the microtubule (MT)-based mitotic spindle captures, aligns, and then equally distributes chromosomes into daughter cells (figure, center). Inhibiting the essential spindle MT dynamics is an effective way to delay or stop exit from mitosis. However, dynamic MTs are also important for cell motility, polarity, and intracellular trafficking. MTs are hollow tubes built from parallel protofilaments of α/β-tubulin heterodimers. MT poisons exert dose-dependent effects on MT dynamics and assembly, blocking MT polymerization (i.e., vinca alkaloids) or depolymerization (i.e., taxanes) at high and suppressing MT dynamics at low concentrations (1). These compounds bind MTs on specific sites: taxanes interact with β-tubulin within the lumen and stabilize the MT, whereas the vinca alkaloid, vinblastine, binds MT ends and the MT outer surface.

MT poisons, in particular taxanes, have been successfully used in the treatment of solid cancers for over 25 yr (figure, right; 1, 2). However, serious side effects such as peripheral neuropathy, caused partly by impaired axonal transport, and drug resistance can limit their clinical utility. Paclitaxel resistance can arise through multiple mechanisms including mutations in β-tubulin, altered expression of β-tubulin isoforms, changes in apoptotic proteins, or overexpression of drug efflux pumps (3). While new generation MT poisons (i.e., epothilones, eribulin, and estramustine) can overcome some of these limitations, the desire to obtain treatments that trigger fewer side effects and work in paclitaxel-resistant tumors had prompted the development of compounds against mitotic kinases and MT motor proteins.

Polo-like kinase 1 (PLK1) and Aurora kinases (AurA and AurB) play pleiotropic roles during mitosis; they are important for mitotic entry and exit, spindle assembly, and also the capture, alignment, and segregation of chromosomes. PLK1 and AurB also improve effectiveness of spindle assembly checkpoint (SAC) signaling, which ensures that replicated sister chromatids are held together until all chromosomes are correctly attached to the spindle. Mitotic kinesins transport cargos (e.g., chromosomes), but can also cross-link and slide MTs, hence fulfilling important functions in spindle assembly. Eg5 facilitates centrosome separation and bipolar spindle formation, whereas Cenp-E mediates chromosome alignment on the metaphase plate. Highly selective inhibitors developed against these targets showed robust cytotoxic activity in preclinical models. Similar to MT poisons, these anti-mitotics cause drug-specific and dose-dependent mitotic phenotypes through disruption of mitotic spindle morphology and MT–chromosome attachment or impairment of SAC (figure, bottom). The ensuing mitotic delay, abortive mitosis, or abnormal chromosome segregation can trigger a range of cellular stresses. Cellular response to these stresses appears to be stochastic, since the fate of individual cells receiving the treatment in the same dish varies. Some undergo mitotic catastrophe (mitotic cell death) and some exit mitosis with subsequent arrest or death in G1, whereas others continue cycling (4, 5).

Despite promising preclinical results, clinical performance of anti-mitotics has been disappointing. As monotherapies in solid tumors, these agents have not advanced beyond phase II trials (6, 7; figure, left). They showed better efficacy in heamatological malignancies, which has been attributed to higher proliferative rates of blood cancers and off-target activities of anti-mitotics against oncogenic drivers. One phase III clinical trial for the AurA inhibitor Alisertib/MLN8237 was recently completed for treatment of peripheral T cell lymphoma (8). Combination therapies could hold more promise with multiple synergistic interactions reported between anti-mitotics and anticancer drugs. Indeed, Plk1 inhibitor combined with LDAC, and Eg5 inhibitor combined with the proteasome inhibitor carfilzomib, are in phase III clinical trials for AML and multiple myeloma, respectively (9).

Why do anti-mitotic therapies compare less favorably with MT poisons at the clinic? First, the number of mitotic cells is surprisingly low in solid tumors; therefore, drugs need to be maintained within the tumor for adequate time periods to eliminate all dividing cells. Paclitaxel and eribulin are retained in tumors for several days, which may not be the case for anti-mitotics. Second, in addition to targeting mitosis, MT poisons disrupt metabolic and signaling pathways by affecting intracellular trafficking in nonmitotic cancer cells. Third, paclitaxel may further impede tumor growth by activating noncancerous cells of the immune system that will directly or indirectly eliminate tumor cells (10). Multipronged antitumor effects cannot be replicated by the highly selective mitotic inhibitors; however, efficacy could be increased by improved pharmacodynamics and pharmacokinetics (i.e., better in-tumor drug retention) and development of predictive biomarkers from clinical trial data. A larger therapeutic window may be achieved by new compounds that target cancer-specific alterations such as centrosome amplification or overexpression of the SAC component Mps1. Unlike the first generation of anti-mitotics that aimed to block mitosis, Mps1 inhibitors cause cell death by triggering extensive chromosome missegregation, and may therefore yield superior clinical results.

Acknowledgments

We express our sincere apology to all authors whose work could not be cited due to space restrictions.

J. Tischer was supported by a Deutsche Forschungsgemeinschaft research fellowship (HA-8069/1-1). F. Gergely is funded by Cancer Research UK (CRUK/A17043).

The authors declare no competing financial interests.

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