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I am submitting the accompanying paper -- "Mps1 directs the assembly of Cdc20-inhibitory complexes during interphase and mitosis to control M phase timing and spindle checkpoint signaling" -- for consideration for the Chairman's Prize.

There is a great deal of interest in the spindle assembly checkpoint (SAC), which delays sister chromatid separation and mitotic exit until all chromosomes have attached to both poles of the spindle. As the SAC is short-lived and highly dynamic, its analysis begs for the development of small-molecule inhibitors that take effect on the same timescale as mitosis itself. In addition to their value as basic research probes, such compounds can also be used to investigate the potential of the SAC as a cancer drug target, either alone or in combination with standard therapies like taxol.

In this study, we used chemical genetics to rapidly and specifically inhibit the human Mps1 kinase, which belongs to an evolutionarily conserved family of SAC regulators. Briefly, we deleted both alleles of the *MPS1* locus from the human genome and replaced it with a mutant kinase that was susceptible to inhibition by bulky purine analogs. Using this novel experimental system, we discovered two new roles of Mps1: First, we show that this kinase regulates the binding of Cdc20 to the anaphase inhibitors Mad2 and BubR1 (creating the "mitotic checkpoint complex" or MCC) during both interphase and mitosis, and in so doing, contributes to the "cytoplasmic timer" that determines the basal length of M phase in unperturbed cells.

Second, we show that Mps1 plays an essential role in recruiting the Bub1 kinase and all downstream SAC effectors at kinetochores. As a consequence, kinetochores in Mps1-inhibited cells no longer signal effectively, both in terms of delaying anaphase and promoting bi-orientation. Both Mps1-dependent pathways delineated by our study were missed in earlier studies where Mps1 was depleted by over 90% using RNAi -- an eloquent testament to the "awesome power" of chemical genetics.

Finally, we overturn the core claim of a recent paper from Geert Kops' laboratory in *Cell* (Jelluma et al., 2008), as we find no evidence that Mps1 controls the activity of Aurora B, using both chemical genetics and gene deletion methods.

Taken together, our findings both advance and rewrite our view of how the SAC operates in human cells. They also provide the entire field with a powerful new tool for probing the SAC in a surgical manner, without collateral inhibition of Aurora B (unfortunately, all previously known SAC-suppressing drugs affect multiple kinases, including Aurora B, making it impossible to dissect SAC regulation as cleanly as we have done here).