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PROJECT TYPE	ERC Starting Grant (FP7)
TITLE	Geometric control of the cell cycle in the fission yeast
ACRONYM	GeometryCellCycle
DURATION	01.09.2010 – 31.08.2015
BUDGET	1 500 000 €

Cell cycle progression is monitored by checkpoints that ensure the fidelity of cell division and prevent unrestricted cell proliferation. Checkpoints also serve to couple cell size with division a mechanism important to adapt to changing environmental conditions. The project GeometryCellCycle aimed to investigate the mechanism and functional importance for cell size regulation of a novel proposed geometry-sensing system. The proposed system was based on the discovery that the DYRK-family protein kinase, Pom1, which forms concentration gradients from the poles of the rod-shaped fission yeast cell, delays mitotic entry by negatively regulating a target kinase, Cdr2, located at mid-cell.

By combining genetic, biochemical, live-imaging and modelling approaches, this project reached three major achievements. First, we defined the molecular mechanisms of Pom1 gradient formation. We showed that Pom1 gradients are nucleated by a local dephosphorylation of Pom1 at the plasma membrane, and shaped by lateral movement in the plane of the membrane and auto-phosphorylation promoting Pom1 release from the membrane. We further showed that Pom1 auto-phosphorylating inter-molecularly provides a simple feedback to buffer activity and ensure gradient shape robustmess to variation. Second, we revealed that Pom1 controls both timing and positioning of cell division through direct phosphorylation of the same substrate Cdr2, but in distinct functional regions, regulating Cdr2's activity and its association with the membrane.

Finally, we established that the Pom1-Cdr2 'geometric' system does not primarily control cell size homeostasis within a single cell cycle, but is rather used to coordinate information on external nutrient availability with cell cycle progression, and thus cell size adaptation to the environment. Indeed, Pom1 mid-cell levels stay roughly constant during a single cell cycle, Pom1 distribution is dramatically affected by growth in low glucose levels, due to destabilization of microtubules, which now deposit Pom1 gradients nucleating factors along cell sides.